Chapter 11
Mathematical Modeling and Trichloroethylene

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Abstract Mathematical modeling has been used extensively to quantify and characterize the disposition, fate, and risk associated with the volatile organic chemical trichloroethylene (TCE). Here, we summarize many of these models that have been developed and applied across the exposure-dose-effect continuum, ranging from pharmacokinetic and pharmacodynamic models to quantitative structure-activity relationships. We conclude by reviewing some future directions in computational modeling that are increasingly used to inform an understanding of the adverse health effects associated with exposure to TCE, and introduce elements of a first-generation systems biology model of TCE-induced autoimmune disease.

Keywords Mathematical modeling • Computational modeling • Exposure • Pharmacokinetics • Pharmacodynamics • QSAR • Systems biology • Omics • Dose response

Acronyms and Abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AIH	Autoimmune hepatitis
ARR	Arrest of mitosis in *Aspergillus nidulans*

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K.M. Gilbert, S.J. Blossom (eds.), *Trichloroethylene: Toxicity and Health Risks*, Molecular and Integrative Toxicology, DOI 10.1007/978-1-4471-6311-4_11,

AUC	Area under the curve
BBDR	Biologically-based dose response
BBPD	Biologically-based pharmacodynamic
BDM	Benchmark dose method
BEI	Biological exposure index
CNS	Central nervous system
CPK	Compartmental pharmacokinetic
D37	Measure of lethality in *Aspergillus nidulans*
DCA	Dichloroacetic acid
DCVC	*S*-(1,2-dichlorovinyl)-L-cysteine
DCVG	*S*-(1,2-dichlorovinyl)glutathione
DIFF	Difference between the highest occupied molecular orbital and the lowest unoccupied molecular orbital
DNAPL	Dense nonaqueous phase liquid
EDR	Exposure-dose-response
EPA	US Environmental Protection Agency
HBA	H-bonding acceptor ability
HBD	H-bonding donor ability
IC50	Chemical concentration that inhibits some endpoint in 50 % of the test animals in a given time
IRIS	Integrated Risk Information System
Kow	Octanol-water partition coefficient
LC50	Chemical concentration that kills 50 % of the test animals in a given time
LCA	Life cycle assessment
LEC	Induction of chromosome malsegregation leading to aneuploidy in *Aspergillus nidulans*
LOEC	Lowest observed effect concentration
logP	The log of the ratio of concentration of neutral species in octanol divided the concentration of neutral species in water
MCL	Maximum contaminant level
MOE	Margin of exposure
MR	Molar refractivity
MRL	Minimal risk level
NAPL	Non-aqueous phase liquid
NCPK	Non-compartmental pharmacokinetic
PBPK	Physiologically-based pharmacokinetic
PC	Partition coefficient
PCE	Tetrachloroethylene, perchloroethylene
PD	Pharmacodynamics
PEL	Permissible exposure limit
PK	Pharmacokinetics
QSAR	Quantitative structure activity relationship
RfC	Reference concentration

$t_{1/2}$	Chemical half life
TAI	TCE-induced autoimmunity
TBARS	Thiobarbituric acid reactive substance
TCA	Trichloroacetic acid
TCE	Trichloroethylene
TCOH	Trichloroethanol
TLV	Threshold limit value
VOC	Volatile organic compound

11.1 Introduction

Mathematical/computational models in toxicology have the potential to integrate information and data from a variety of sources to help in the prediction and understanding of the adverse health effects caused by exposure to foreign chemicals (xenobiotics); moreover, mathematical modeling can provide researchers and practitioners with a "virtual lab" in which to explore hypotheses, conduct complex multifactorial studies that would be impractical or impossible using conventional experimental techniques, and rapidly analyze, extrapolate, and evaluate results, all while reducing the need for animal experimentation. Further, these models can be used to investigate the interactions of chemical agents and biological organisms across many scales (e.g., population, individual, cellular, and molecular) and may be used to inform the hazard and risk prioritization of chemicals (Reisfeld and Mayeno 2012a, b).

In this chapter, we review many of the mathematical models and approaches that have been used to analyze and quantify the exposure-dose-effect continuum (National Center for Environmental Assessment 2011) for trichloroethylene (TCE). As shown in Fig. 11.1, these include models for exposure, pharmacokinetics, pharmacodynamics, and quantitative structure activity relationships. We conclude the chapter with a summary of several future directions in modeling and then introduce a potential approach to developing a systems biology model describing TCE-induced autoimmune hepatitis.

Although the modeling of the source, emission, and transport of TCE (Brusseau et al. 2007, 2012; Asher et al. 2007; Chambon et al. 2010, 2011; Johnson et al. 2003; Pederson et al. 2001; Atteia and Höhener 2010; Reynolds and Kueper 2001; Oostrom et al. 1999; McKone 1996; Clement et al. 1998; Cohen and Ryan 1985) are important considerations in an overall chemical risk assessment, those modeling aspects and approaches are not covered here. Moreover, the references cited in the following sections are not intended to be comprehensive, but are representative of the body of work in each modeling category. Many additional references are available in the scientific literature and in the excellent comprehensive risk assessment (Environmental Protection Agency 2001) and Integrated Risk Information System (IRIS) (Environmental Protection Agency 2011) for TCE.

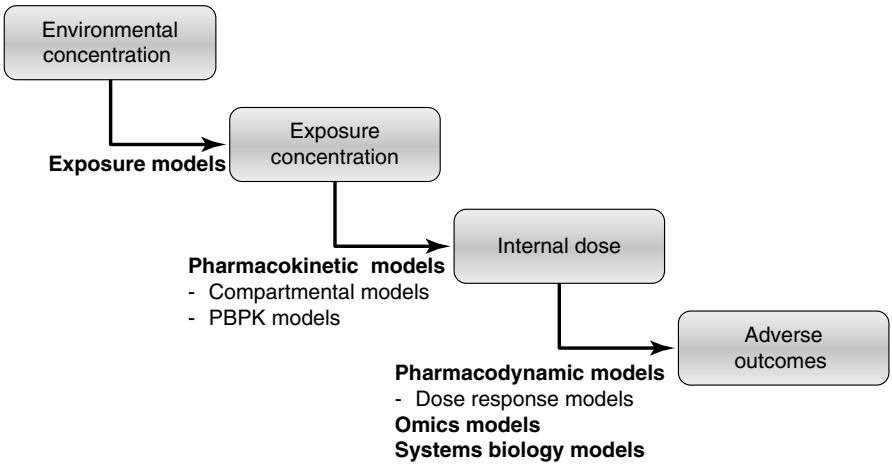

Fig. 11.1 Computational models relevant at each stage along the exposure-dose-effect continuum

11.2 Exposure Models

Exposure is the contact between a contaminant or pollutant and an individual or population through environmental media, such as air, water, soil, dust, and food. The modeling of exposure focuses on the prediction and quantitative description of the spatial and temporal characteristics of this contact. Thus, exposure modeling can be used to help inform our understanding of how the properties of chemical contaminants and the media and pathways in which they move affect pollutant exposure, and can provide quantitative measures of this exposure that can then be used to estimate dose and other metrics useful for risk assessment.

A number of computational models have been developed and utilized to simulate exposure to TCE through various environmental media. In particular, several studies have employed computational models to assess the impact of the transport and release of TCE from source zones above and below the water table into indoor air. Vapor intrusion, in which TCE vapors move from contaminated groundwater and soil into the indoor air of overlying buildings, is an significant route of environmental exposure (Office of Solid Waste and Emergency Response 2012). Yu and coworkers (2009a) used the multi-phase compositional model CompFlow Bio (Yu et al. 2009b) to simulate the transport of TCE into the indoor air of residential dwellings from a dense non-aqueous phase liquid (DNAPL) source zone located below the water table. Of interest in these studies was the role of heterogeneity in the subsurface permeability structure of the aquifer and a determination of the relative importance of variability in factors such as source zone location and pressure drop within the dwelling. Through model simulations, these investigators found that the simulated indoor air concentrations of TCE were extremely sensitive to assumptions made about the aquifer heterogeneity and that pressure fluctuations in the soil gas beneath the foundation slab had a significant effect on these contaminant

concentrations. Motivated by the desire to simulate indoor air concentrations of TCE in houses with locations that were offset from the groundwater plume flow, Wang et al. (2012) extended the above analysis of Yu et al. to include a fully three-dimensional geometry. Following a similar set of simulation and sensitivity studies using CompFlow Bio (Yu et al. 2009b), these researchers determined that houses that are laterally offset from the groundwater plume are less affected by vapor intrusion than those located directly above the plume. They also noted that characterizing the site stratigraphy is a first-order priority when attempting to assess the impact of the fate and transport of TCE from an observed source zone to the indoor air.

Although the above studies examined exposure to TCE through multiple environmental media, other studies have focused on exposure to this pollutant through air alone. In particular, to better understand and quantify non-occupational exposure to TCE and other VOCs, Sexton et al. (2007) developed a new modeling approach to estimate the concentrations of these pollutants in five relevant microenvironments: indoors at home, indoors at work/school, indoors in other locations, outdoors in any location, and in transit. Employing hierarchical Bayesian techniques, they predicted that concentrations would be highest in "other" indoor microenvironments, intermediate in the indoor work/school and residential microenvironments, and lowest in the outside and in-transit microenvironments. Based on a series of comparisons with biomonitoring measurements, they found that predicted concentrations of all VOCs examined were in reasonable agreement with experimental median concentrations in the indoor residential microenvironment. They further suggested that since personal monitoring is often impractical in many situations, their modeling approach would be a promising alternative for estimating VOC concentrations in seldom monitored microenvironments.

In the context of general biomonitoring of TCE exposure through the air, Droz and Fernández (1978) used their previously developed pharmacokinetic model (Fernández et al. 1977) to investigate the impact of biomarker selection and sample collection timing on predicted exposure. Based on results of systematic model simulations, they found that for maximum usefulness, sampling and analysis of alveolar air for TCE and trichloroethanol (TCOH) must be carried out at least 6 h after the end of the exposure. In contrast, they noted that the timing for the collection and analysis of urine for trichloroacetic acid (TCA) was unimportant, but also suggested that this biomarker is of limited value for the biological monitoring of exposure because of its lack of sensitivity as an indicator of a single exposure to TCE.

Another area in which the use of mathematical models has provided quantitative information and insights into the risks of TCE is the estimation of exposure to this chemical at or near hazardous waste sites. Using a combination of computational modeling techniques, Maslia et al. (1996) conducted a health assessment for the Gratuity Road site in the town of Groton, Massachusetts, which had been contaminated with TCE and several other environmental pollutants. These researchers first used an environmental transport model to create a spatial and temporal mapping of pollutant concentrations and flow in the region. They next used these contaminant levels to carry out a computational analysis of probable exposures routes and levels. Based on these studies, Maslia and coworkers concluded that (i) predicted

groundwater concentrations of TCE in the area typically exceeded the US Environmental Protection Agency (EPA) value for the maximum contaminant level (MCL) for TCE, (ii) despite direct remediation of the waste site, historical contamination can cause nearby populations to experience significant exposure, and (iii) because the predicted exposure to TCE through inhalation during showering was nearly identical to that through ingestion of contaminated domestic water, both of these routes should be considered when conducting exposure analyses of contamination from VOCs such as TCE.

Using a different exposure modeling methodology, Johnston and Gibson (2011) estimated residential indoor air concentrations of TCE and perchloroethylene (PCE) resulting from plumes of groundwater contamination from the former Kelly Air Force Base in San Antonio, Texas. For this study, the authors developed a probabilistic exposure model, based on the Johnson-Ettinger algorithm (Johnson and Ettinger 1991), and compared predicted results with measurements taken in a subset of homes in the affected area. From these comparisons, they noted that the model systemically underestimated high exposures, but that the 95th percentile of the predicted value would be a more useful indicator of the risk. An overall analysis of simulation results and sampling data led these researchers to conclude that homes above the contaminant groundwater plume surrounding the Kelly Air Force Base are still at risk of vapor intrusion and that the probabilistic approach used in their model could better identify priority areas for further sampling than current deterministic approaches.

11.3 Pharmacokinetic Models

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion (ADME) of xenobiotics. Pharmacokinetics (PK) is frequently referred to as "what the body does to the chemical". Models of pharmacokinetics are often designed to answer questions like "Given a dose of a chemical, where does it go in the body, what is the time-course blood or tissue concentration of the parent chemical and/or its metabolites, and how quickly is it metabolized and eliminated?". PK models are also used to compute derived quantities, such as the chemical clearance, area under the curve (AUC), and half-life ($t_{1/2}$). In the context of toxicant exposure, pharmacokinetics are often referred to as toxicokinetics. Pharmacokinetic modeling is critical in the field of toxicology because it allows investigators to predict time-dependent quantities that are highly relevant in assessing chemical toxicity: biodistribution, internal dose, and clearance.

There are several types of pharmacokinetic models that have been created and used to predict chemical disposition:

(i) non-compartmental pharmacokinetic (NCPK) models: These models are useful for the estimation of certain PK parameters, such as area under the curve (AUC), and half-life ($t_{1/2}$). NCPK approaches use mathematical and statistical techniques to derived these parameters using a minimal amount of experimental

data (typically, chemical levels in the blood or plasma over time). However, since they do not contain mechanistic underpinnings, such models are not useful for any type of extrapolation. Non-compartmental models have been applied extensively for drugs, but their utility in toxicology is limited and hence are not discussed here.

(ii) compartmental pharmacokinetic (CPK) models: By "lumping" major tissues, organs, or regions of the body together, these models treat the body as one or more compartments comprising "apparent volumes of distribution" (Shen 2007) (conventionally, the dose administered divided by the resultant plasma concentration). CPK models typically require data on concentration of the chemical species over time in the blood and use that information to estimate certain kinetic parameters related to transport and elimination within and between the compartments. In general, like NCPK models, CPK models are not useful outside of the datasets for which they have been developed and will not be useful for extrapolations across individuals and doses.

(iii) physiologically-based pharmacokinetic (PBPK) models: In contrast to NCPK and CPK models, physiologically based pharmacokinetic (PBPK) models incorporate the anatomical entities and physiological and biochemical processes of organisms. Because of this, PBPK models can be used to perform inter-species, inter-route, and/or inter-dose extrapolations and to describe concentration-time profiles in individual tissues or organs and in the plasma or blood. While PBPK models can provide a wealth of information, they require extensive data for parameterization and validation, including anatomical, physiological, and biochemical data, as well as experimentally-derived time-course concentration levels in multiple tissues, ideally at varying dose levels and routes of exposure. The need for this amount and detail of information makes PBPK modeling impractical and/or overly burdensome in many situations.

11.3.1 Compartmental Pharmacokinetic Models

To date, there have been few CPK models constructed for the analysis of TCE pharmacokinetics. Nevertheless, one such model was constructed by Kim et al. (2009) to characterize and quantify the pharmacokinetics of TCE metabolites in male B6C3F1 mice exposed to TCE. Specifically, these researchers created a two-compartment model to predict the time course concentrations of TCE, TCA, dichloroacetic acid (DCA), *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), and *S*-(1,2-dichlorovinyl)glutathione (DCVG) formation, and used data acquired from a novel analytical method to calibrate and validate the model. The authors found that following calibration, model predictions agreed well with the acquired data, and through a mechanistic pathway analysis, suggested that TCE-oxide is the most likely source of the hepatotoxicant DCA. They concluded by noting that the results of their analyses could be used to reassess existing models of TCE and ultimately inform the risk assessment for this important chemical.

11.3.2 Physiologically-Based Pharmacokinetic Models

Aside from its use in predictive tissue dosimetry described above, PBPK models have been used for a large variety of applications (Reisfeld et al. 2007, 2013; Reddy et al. 2005; Lyons et al. 2008; Bois et al. 1996; Bois 2000; Hack et al. 2006; Caldwell et al. 2012), including risk assessment, development of dose metrics, biomarker characterization, regulatory review, chemical prioritization, chemical mixture toxicity assessment, uncertainty and variability analyses, and dose reconstruction.

A large number of PBPK models for TCE have been developed for virtually all of the above applications. Table 11.1 contains an extensive list of many of these models and their principal features. Some of the distinctive classes of PBPK models listed are in the areas of cancer and cancer risk assessment (Clewell et al. 1995, 2000; USAF-EPA TCE PBPK workgroup 2004; Evans et al. 2009; Chiu 2011; Cronin et al. 1995), non-cancer effects and risk assessment (Clewell et al. 1997, 2000; Barton and Clewell 2000; Simmons et al. 2005; Fisher and Allen 1993; Bushnell et al. 2005), development of acute exposure guidelines (Bruckner et al. 2004; Boyes et al. 2005), equation and data harmonization (Hack et al. 2006; USAF-EPA TCE PBPK workgroup 2004), combined pharmacokinetic/pharmacodynamic models (Clewell et al. 1997; Bushnell et al. 2005; Clewell and Andersen 1994; Simon 1997), and population effects (Bois 2000; Hack et al. 2006; Simon 1997; Sohn et al. 2004; Chiu et al. 2009).

One of the most recent and comprehensive models is that of Chiu and coworkers (2009). The modeling framework developed by these investigators comprises a PBPK model for TCE and its major metabolites (see Fig. 11.2) and uses Bayesian inference to account for population variability and experimental and model uncertainty. In developing, calibrating, and validating this model, they used data from mice, rats, and humans, and considered a wider range of physiological, chemical, *in vitro*, and *in vivo* data than any previously published analysis of TCE. Owing to the above features, this PBPK model may represent the most complete, and thoroughly parameterized and validated, PBPK model for TCE to date.

11.4 Pharmacodynamic Models

Pharmacodynamics is the study of the biochemical and physiological effects of xenobiotics and the mechanisms of their actions. Pharmacodynamics (PD) is frequently referred to as “what the chemical does to the body”. Models of pharmacodynamics incorporate information about how, and to what extent, the toxicant and/or its metabolites interact with relevant biomolecules or structures (e.g., receptors, enzymes, macromolecules, membranes). These models are often designed to answer questions like “Given a concentration (internal dose) of a chemical contaminant at some site of action, what is the level of the biological response over time and how does this response depend on the internal dose?”. For example, a researcher interested in understanding the carcinogenic potential of a new chemical may develop a

Table 11.1 Physiologically-based pharmacokinetic (PBPK) models for trichloroethylene

Year	Study authors	Modeling features	Reference
1987	Andersen, Gargas, Clewell, and Severyn	Simulation of gas uptake studies for TCE and 1,1-dichloroethylene (1,1-DCE) in male Fischer 344 rats using PBPK modeling	Andersen et al. (1987)
1989	Koizumi	Amalgamation of information obtained in rats and man by various routes of exposure to TCE and PCE using PBPK modeling	Koizumi (1989)
1990	Fisher, Whittaker, Taylor, Clewell, and Andersen	Prediction of TCE kinetics in a lactating rat and nursing pup using PBPK modeling	Fisher et al. (1990)
1991	Sato, Endoh, Kaneko, and Johanson	Investigation of the effect of physiological factors on the pharmacokinetic behavior of inhaled TCE	Sato et al. (1991)
1991	Staats, Fisher, and Connolly	Simulation of TCE, methylene chloride, chloroform, and dichloroethane toxicokinetics using a two-compartment description of GI absorption	Staats et al. (1991)
1993	Allen and Fisher	Prediction of TCE and TCA disposition in humans using PBPK modeling	Allen and Fisher (1993)
1993	Fisher and Allen	Simulation of gavage and inhalation bioassays with TCE using PBPK modeling and linkage with plausible dose-metrics for carcinogenesis	Fisher and Allen (1993)
1994	Clewell and Andersen	Overview of several PBPK models, including one for TCE	Clewell and Andersen (1994)
1995	Barton, Creech, Godin, Randall, and Seckel	Simulation of the pharmacokinetics of a mixture of TCE and vinyl chloride in rats using a PBPK model	Barton et al. (1995)
1995	Clewell, Gentry, Gearhart, Allen, and Andersen	Cancer risk estimation for human exposure to TCE using a PBPK model coupled with a linearized multistage model	Clewell et al. (1995)
1995	Cronin, Oswald, Shelley, Fisher, and Flemming	Risk assessment for TCE using a PBPK model coupled with a linearized multistage model to derive human carcinogenic risk extrapolations	Cronin et al. (1995)
1996	El-Masri, Constan, Ramsdell, and Yang	Investigation of an interaction threshold between TCE and 1,1-dichloroethylene in Fischer 344 rats using PBPK modeling	el-Masri et al. (1996a)
1996	El-Masri, Tessari, and Yang	Investigation of mechanism of interaction between TCE and 1,1-dichloroethylene using data from gas uptake experiments and a PBPK model	El-Masri et al. (1996b)

(continued)

Table 11.1 (continued)

Year	Study authors	Modeling features	Reference
1996	Thomas, Bigelow, Keefe, and Yang	Comparison of simulations results with existing biological exposure indices (BEIs) for six industrial solvents (TCE, benzene, chloroform, carbon tetrachloride, methylene chloride, methyl and chloroform) using PBPK and Monte Carlo modeling.	Thomas et al. (1996)
1997	Abbas and Fisher	Simulation of the pharmacokinetics of TCE and its metabolites in the B6C3F1 mouse using a six-compartment PBPK model	Abbas and Fisher (1997)
1997	Bogen and Gold	Prediction of maximum concentration level for cytotoxic end points using PBPK modeling	Bogen and Gold (1997)
1997	Clewell, Gentry, and Gearhart	Non-cancer risk assessment incorporating both mechanistic and delivered dose information using a PBPK model along with the benchmark dose method	Clewell et al. (1997)
1997	Simon	Simulation of occupational exposure to TCE using Monte Carlo population distribution sampling and PBPK modeling	Simon (1997)
1998	Fisher, Mahle, and Abbas	Prediction of blood, urine, and exhaled breath concentrations using PBPK modeling and comparison to data from human volunteers	Fisher et al. (1998)
1998	Lipscomb, Fisher, Confer, and Byczkowski	Extrapolation of TCE pharmacokinetics to humans using in vitro data and a PBPK model	Lipscomb et al. (1998)
1998	Stenner, Merdink, Fisher, and Bull	Investigation of the role of enterohepatic recirculation on the pharmacokinetics of major metabolites of TCE using PBPK modeling	Stenner et al. (1998)
1999	Greenberg, Burton, and Fisher	Prediction of the disposition of inhaled TCE for mice; PBPK model contains submodels for chloral hydrate, free and glucuronide-bound TCOH, TCA, and DCA	Greenberg et al. (1999)
2000	Bois	Estimation of both variability between experimental groups and uncertainty in toxicokinetics using Bayesian analyses of a PBPK model for rodents and humans, including	Bois (2000)
2000	Barton and Clewell	Utilization of a PBPK model within a framework for evaluation of chronic exposure limits for non-cancer effects	Barton and Clewell (2000)
2000	Clewell, Gentry, Covington, and Gearhart	Prediction of the kinetics of TCE, TCOH, and TCA, in the mouse, rat, and human using a PBPK model, for both oral and inhalation exposure; dose metrics provided for cancer risk assessment	Clewell et al. (2000)

Table 11.1 (continued)

Year	Study authors	Modeling features	Reference
2002	Albanese, Banks, Evans, and Potter	Investigation of TCE pharmacokinetics in adipose tissue using three different PBPK models	Albanese et al. (2002)
2002	Dobrev, Andersen, and Yang	Simulation of interaction thresholds for human exposure to mixtures of TCE, PCE, and methyl chloroform using PBPK modeling	Dobrev et al. (2002)
2002	Hissink, Bogaards, Freidig, Commandeur, Vereulen, and van Bladeren	Risk assessment for TCE using *in vitro* metabolic parameters and PBPK modeling	Hissink et al. (2002)
2002	Simmons, Boyes, Bushnell, Raymer, Limsakun, McDonald, Sey, and Evans	Evaluation of neurotoxicity data aided by the development of a PBPK specifically for the Long Evans rat	Simmons et al. (2002)
2003	Keys, Bruckner, Muralidhara, and Fisher	Expansion and extensive tissue dosimetry validation of rodent PBPK models for TCE exposure	Keys et al. (2003)
2004	Bruckner, Keys, and Fisher	Estimation of acute exposure guideline levels based on PBPK model predictions of time course concentrations for TCE in the blood and/or brain of rats and humans	Bruckner et al. (2004)
2004	Clewell and Andersen	Estimate target tissue doses for the three principal animal tumors associated with TCE exposure (liver, lung, and kidney) using PBPK modeling	Clewell and Andersen (2004)
2004	Isaacs, Evans, and Harris	Investigation of the mechanism of metabolic interactions during simultaneous exposures to TCE and chloroform using a PBPK model incorporating mixed enzyme inhibition	Isaacs et al. (2004)
2004	Sohn, McKone, and Blancato	Identification of some of the difficulties in reconstructing population-scale exposures when using Bayesian inference and PBPK models	Sohn et al. (2004)
2004	USAF-EPA TCE PBPK workgroup	Prediction of the kinetics of TCE, TCOH, and TCA, in the mouse, rat, and human, for both oral and inhalation exposure; dose metrics provided for cancer risk assessment	USAF-EPA TCE PBPK workgroup (2004)
2005	Beliveau and Krishnan	Simulation of the pharmacokinetics of inhaled TCE and other VOCs in humans using a spreadsheet-based PBPK model, and the estimation of its parameters based on quantitative structure-property relationships (QSPRs)	Béliveau and Krishnan (2005)

(continued)

Table 11.1 (continued)

Year	Study authors	Modeling features	Reference
2005	Boyes, Evans, Eklund, Janssen, and Simmons	Development of acute exposure guideline level recommendations for various exposure durations and levels of severity using arterial blood concentrations predicted using a PBPK model	Boyes et al. (2005)
2005	Bushnell, Shafer, Bale, Boyes, Simmons, Eklund, and Jackson	Prediction of the neurotoxicity of TCE and other VOCs using an exposure–dose–response (EDR) model comprising a PBPK model linked to a toxicodynamic component	Bushnell et al. (2005)
2005	Simmons, Evans, and Boyes	Determination of dose metrics predictive of the acute neurotoxic effects of TCE using PBPK modeling	Simmons et al. (2005)
2006	Hack, Chiu, Jay Zhao, and Clewell	Population analysis of a harmonized PBPK model for TCE using Bayesian inference	Hack et al. (2006)
2006	Haddad, Tardif, and Tardif	Characterization of the influence of different routes of exposure to volatile organic chemicals present in drinking water using PBPK models for trihalomethanes and TCE	Haddad et al. (2006)
2007	Liao, Tan, and Clewell	Estimation of exposures to volatile organic compounds that correspond to levels measured in fluids and/or tissues using a generic PBPK model coupled with exposure pattern characterization, Monte Carlo analysis, and quantitative structure property relationships	Liao et al. (2007)
2007	Rodriquez, Mahle, Gearhart, Mattie, Lipscomb, Cook, and Barton	Prediction of age-appropriate pharmacokinetics of TCE, PCE, benzene, chloroform, methylene chloride, or methyl ethyl ketone in the rat utilizing physiologically based pharmacokinetic modeling	Rodriguez et al. (2007)
2007	Yokley and Evans	Evaluation and comparison of two alternative PBPK models for TCE based on parameter sensitivity analyses	Yokley and Evans (2007)
2008	Easterling, Evans, and Kenyon	Comparison of SimuSolv and MATLAB for PBPK modeling of TCE	Easterling et al. (2000)
2008	Li, Schultz, Keys, Campbell, and Fisher	Prediction of dichloroacetic acid (DCA) biotransformation and kinetics in humans administered DCA by intravenous infusion and oral ingestion using PBPK modeling	Li et al. (2008)
2009	Chiu, Okino, and Evans	Development of a comprehensive, Bayesian, PBPK model-based analysis of the population toxicokinetics of TCE and its metabolites in mice, rats, and humans, considering a wider range of physiological, chemical, in vitro, and in vivo data than any previously published analysis of TCE	Chiu et al. (2009)

Table 11.1 (continued)

Year	Study authors	Modeling features	Reference
2009	Evans, Chiu, Okino, and Caldwell	Investigation of the role of TCA in the liver in TCE-induced hepatomegaly in mice using PBPK modeling and exposure data for TCE, TCA, and DCA.	Evans et al. (2009)
2010	Chen, Shih, and Wu	Estimation of inhalation exposure to TCE using a PBPK model based on repeated measurements in venous blood along with a hierarchical Bayesian approach	Chen et al. (2010)
2010	Csanády, Göen, Klein, Drexler, and Filser	Development of a two-compartment PBPK model to simulate the disposition of the TCE metabolite TCA based on concentration of inhaled TCE in humans	Csanády et al. (2010)
2011	Chiu	Analysis of the role of TCA in hepatomegaly by PBPK modeling that incorporates non-linear changes in internal TCA dose due to dose-dependent fractional absorption	Chiu (2011)
2011	Price and Krishnan	Prediction of the inhalation toxicokinetics of chemicals in a mixture containing TCE using an integrated QSAR-PBPK modeling approach	Price and Krishnan (2011)
2011	Valcke and Krishnan	Assessment of the impact of exposure route on the human kinetic adjustment factor used in non-cancer risk assessment using a multi-route PBPK model appropriate TCE and several other VOCs	Valcke and Krishnan (2011)
2012	Chen, Shih, and Wu	Reconstruction of exposure to TCE using a physiologically based toxicokinetic model with cumulative amount of metabolite in urine	Chen et al. (2012)
2012	Mumtaz, Ray, Crowell, Keys, Fisher, and Ruiz	Evaluation of minimal risk levels for volatile organic compounds, including TCE, using a generic seven-compartment PBPK model	Mumtaz et al. (2012)

PD model to predict DNA adduct levels as a function of the internal dose of this compound. In the context of toxicant exposure, pharmacodynamics are often referred to as toxicodynamics.

As described below, pharmacodynamic models for TCE have focused on predictions for both cancer and non-cancer endpoints. In addition, a number of studies related to TCE risk assessment have utilized pharmacodynamic models coupled to pharmacokinetic components (Clewell et al. 1997; Bushnell et al. 2005; Clewell and Andersen 1994; Simon 1997); these studies are not described in this section, but were discussed previously (*vide supra*) and/or are listed in the PBPK model table (Table 11.1).

To delineate and quantify the effects of TCE on oxidative stress in the liver, Byczkowski and coworkers (1999) developed a biologically based pharmacodynamic (BBPD) model. Focusing on chemically-induced lipid peroxidation (a process associated with nephrotoxicity (Cojocel et al. 1989), autoimmune diseases

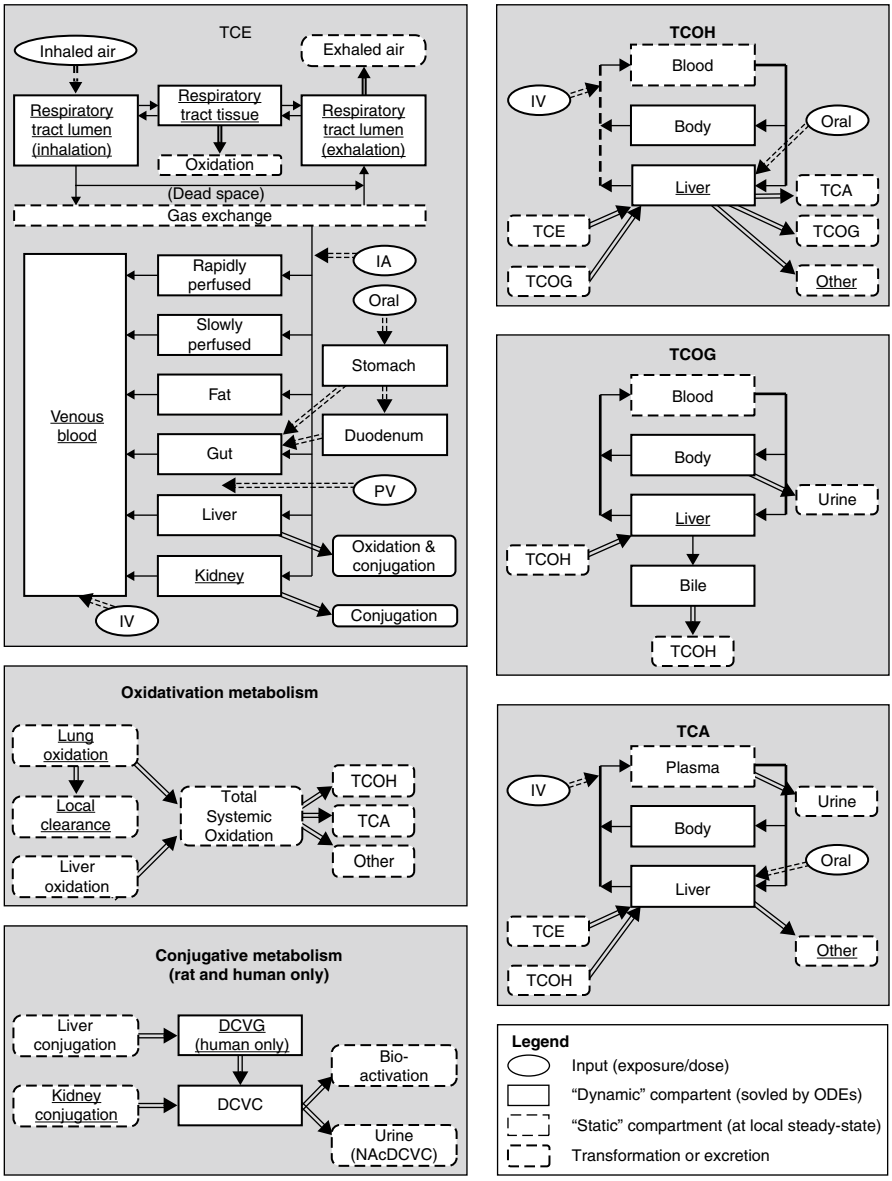

Fig. 11.2 Structural diagram for the comprehensive PBPK model for TCE and its metabolites developed by Chiu et al. (2009) (Adapted with permission)

(Wang et al. 2007), and other adverse health effects (Hu et al. 2008)), they updated a previous mathematical model (Byczkowski et al. 1996) to describe the kinetics and dose response induced by TCE *in vivo*. This model had several unknown parameters that were determined experimentally using an *in vitro* system in which

precision-cut mouse liver slices were exposed to TCE vapors and the lipid peroxidation was quantified using an assay for thiobarbituric acid reactive substances. Through a series of simulations and comparisons to available data, these researchers concluded that their BBPD model adequately described both the PK and PD of TCE-induced lipid peroxidation. When fully validated, we anticipate that models such as this one will have the potential to provide researchers with tools to evaluate and quantify the effect of TCE dose on oxidative stress in the liver.

Unlike the non-cancer endpoint study just described, the work of Chen (2000) focused on developing a dose-response model for liver tumors induced by TCE. This biologically-based dose-response (BBDR) model was constructed using the general approach of Cohen and Ellwein (1990) and the stochastic models of Chen and Farland (1991) and Tan and Chen (1995). According to the study author, the utility of such a model could be to quantitatively describe TCE, DCA, and TCA bioassay results, clarify the role of these compounds on tumor induction, and evaluate how interactions among these chemicals could potentially impact low-dose extrapolation. By comparing model simulations and literature data on tumor incidence, Chen demonstrated that DCA could be responsible for most of the tumor response found in TCE and TCA bioassays. Aside from this important result, the author clarified the importance of biological assumptions on low-dose risk estimates, and emphasized the need for more flexible BBDR models and further laboratory studies to clarify the biological processes underlying dose-response relationships for TCE.

11.5 Quantitative Structure Activity Relationships

Quantitative structure activity relationships (QSARs) are mathematical models that link the structural characteristics of a chemical with its chemical or biological activity (Hansch and Leo 1995). When QSARs are used for property predictions, they are often called quantitative structure property relationships (QSPRs). The structural characteristics, or descriptors, are generally electronic, geometrical, topological, or constitutional properties of the molecule, while the biological activity is typically a physicochemical property of the molecule or some appropriate toxicological/pharmacological endpoint. For example, suppose that a researcher is interested in determining a measure of acute toxicity (LD50) for a large family of chemical congeners. One approach would be to experimentally determine this value for each chemical. This could be quite laborious, and each new chemical of interest would have to be tested. Another approach would be to (i) determine the value of LD50 for only certain of the congeners, (ii) identify easily-calculated chemical properties of the congeners that are good predictors (descriptors) of LD50 [say lipophilicity (logP), molar refractivity (MR), H-bonding acceptor ability (HBA), and H-bonding donor ability (HBD)], and (iii) create a mathematical correlation to predict LD50 based on these descriptors, e.g., $LD50 = \alpha * \log P + \beta * MR + \chi * HBA + \delta * HBD$, where α, β, χ, δ would be determined from the experimental data obtained for

the limited set of congeners. If the chosen descriptors and correlation form were appropriate, this equation could be used to predict the unknown values of LD50 for all of the remaining congeners.

QSAR models have been developed in several areas related to TCE pharmacokinetics and pharmacodynamics. In particular, for pharmacokinetic applications QSARs have been used to estimate a number of essential physicochemical parameters, such as the partition coefficient (PC). The PC, which depends on the properties of both the chemical and the tissue, is the ratio of the equilibrium concentration of the chemical in the tissue to that in the blood or plasma. Payne and Kenny (2002) examined a number of QSAR equations for calculating blood-air, tissue-air, or tissue-blood partition coefficients of TCE and other volatile organic chemicals in human and rat tissues. By comparing the predictions from several published empirical, non-empirical (tissue composition-based), and semi-empirical equations for tissue-air and tissue-blood PCs in humans and rats, they concluded that (i) some of the model equations could be used to estimate human blood–air PCs, but that predictions for the rat (for which chemical binding with blood proteins was significant) were not well predicted by any of the equations, (ii) tissue–blood PCs were most accurately estimated for most chemicals by empirical equations, and (iii) no single choice of model equation was best under all circumstances and that the appropriate choice will depend on the chemical, tissue, and species of interest.

Another study involving the application of QSARs to PK analyses was conducted by Price and Krishnan (2011), who developed an integrated QSAR-PBPK modeling approach to predict the inhalation toxicokinetics of chemicals in TCE-containing mixtures. One of the major aims of the study was to use QSARs to estimate many of the model parameters for which experimental studies were usually required. In particular, the authors determined PCs and kinetic parameters for metabolism (V_{max} and K_m) based solely on chemical structure using a group contribution approach. They then used these estimated parameters within an interaction-based PBPK models to predict the ADME of chemicals in mixtures of up to ten components. Despite some apparent inaccuracies in the parameter estimates, the study authors concluded that their integrated modeling methodology was useful for initial assessments of the pharmacokinetics of components within chemical mixtures.

A limited number of studies have employed QSAR modeling to analyze and characterize the pharmacodynamics associated with TCE exposure. One such study was conducted by Niederlehner et al. (1998) who developed QSAR models to predict the response of the daphnid *Ceriodaphnia dubia* to six widely used industrial chemicals, including TCE. In particular, these investigators developed QSARs to relate relevant endpoints [lethal concentration (LC50) at 2 days and reproductive impairment (reproductive IC50)] with the octanol-water partition coefficient (Kow) for the chemical or chemical mixture of interest. The authors also constructed a QSAR to predict the toxicity of the applied chemical mixture as a function of the mixture composition. Based on the study results, they determined that the QSARs developed seemed consistent with those created by other investigators for other species of daphnid, and that while a predictive dose-additive relationship overestimated toxicity for the chemical mixtures, the fitted (QSAR) models were more consistent with the observed results.

Aside from predictions of endpoints related to acute toxicity, QSARs have been constructed and applied for the prediction of the genotoxicity of many chemicals (Worth et al. 2013). For example, Parry et al. (1996) utilized QSAR modeling to analyze the chromosome malsegregation in *Aspergillus nidulans* by a structurally-related series of halogenated hydrocarbons, including TCE. To develop the QSARs, these researchers correlated three endpoints of interest [induction of chromosome malsegregation leading to aneuploidy (LEC), arrest of mitosis (ARR), and lethality (D37)] to two chemical descriptors [the molar refractivity (MR) and the difference between the highest occupied molecular orbital and the lowest unoccupied molecular orbital (DIFF)] using a set of training compounds. Following this parameterization, they used these QSARs to predict the activities of an unrelated test set of congeneric chemicals. Based on these and other validations, the study authors concluded that the models developed were highly effective in their ability to predict the activity of previously untested chemicals, but also noted that the potential to use this QSAR-based approach to predict the activity of aneugenic chemicals in higher organisms is presently unknown.

11.6 Future Directions

There are a number of scientific, economic, and societal factors motivating a transformation in chemical risk assessment from one that relies heavily on data generated through the dosing of experimental animal, to one in which virtually all routine toxicity testing would be conducted *in vitro* by evaluating the response of human cells or cell lines in a series of high-throughput, toxicity pathway assays (National Research Council 2007). A key element in enabling such a transformation will be the development and use of computational modeling tools in the fields of "omics" and systems biology to help organize, analyze, integrate, and augment these assay data (Raunio 2011).

11.6.1 "Omics" Models

Omics refers to the scientific disciplines and collective technologies involved in analyzing the roles and actions of molecules within various cellular "omes", such as the genome, proteome, and metabolome (Mayer 2011). Computational models in this field seek to organize experimental omics data, simulate interactions within and between components of the system, help to decipher relevant biology, and predict outcomes of perturbations to the system.

Genomic modeling focusses on developing and using computational tools and methods to understand and interpret genome sequences, including such diverse techniques as phylogenetic analysis, biosequence analysis, and gene expression data analysis (Koonin 2001; Luscombe et al. 2001). These complex approaches are data intensive and can benefit from the structure provided by modeling. For example,

biosequence analysis examines the structure or function of DNA, RNA or peptide sequences in order to answer questions about sequence homology, regulatory elements, single nucleotide polymorphisms (SNPs) and other features. The methods used for sequence analysis are quite diverse, but all generate large amounts of data. A genome-wide association study to examine SNPs can generate one billion genotypes. Modeling can help researchers to organize, synthesize, analyze, and interpret this vast array of diverse data.

Although few genomic models have been developed in the context of TCE exposure, one such study was conducted by Kim et al. (2011), who conducted a large-scale gene expression analysis on animals exposed to TCE and two other VOCs (dichloromethane and ethylbenzene). A principal aim of this study was to determine if characteristic molecular signatures could be derived for each toxicant from gene expression profiles. Through the use of gene expression analysis, the study investigators were able to find such molecular signatures and identify many genes that could be used to discriminate between VOC-exposed animals and healthy controls. The authors concluded that such expression signatures could be used as surrogate markers for detecting and characterizing biological responses to VOC exposure in the environment.

Metabolomic modeling centers on describing and quantifying the metabolic pathways and spatially- and temporally-varying inventory of metabolites in cells, tissues, organs, or organisms, and linking this information to specific disease states or toxic insults. To date, the only model of this type for TCE is that of Mayeno et al. (2005), who developed a computer-based simulation tool, BioTRaNS (biochemical tool for reaction network simulation), that predicts metabolites from exposure to multiple chemicals and interconnects their metabolic pathways. In this study, the investigators used TCE and three other common drinking water pollutants (PERC, methyl chloroform, and chloroform) as test cases, and through a combination of simulations, discovered new interconnected metabolic pathways and previously-unreported metabolites, predicted reactive intermediates, such as epoxides and acid chlorides, and uncovered points in the metabolic pathways where typical endogenous compounds, such as glutathione or carbon dioxide, were consumed or generated. Example predicted metabolic pathways for a mixture of the four test chemicals using a simplified set of reaction rules are shown in Fig. 11.3; for results using more complete reaction rules, see the original publication (Mayeno et al. 2005). Aside from the results obtained in this particular study, the study authors suggested that BioTRaNS has the potential to aid in risk assessment and provide new and important insights into metabolites and the interrelationship between diverse chemicals that may remained unnoticed through experimentation alone.

11.6.2 Systems Biology Models

In contrast to omics, systems biology centers on an *integration* of data from multiple levels of complexity *across* "omes" into a "systems view" of biological and pathological processes. In the field of toxicology, systems biology frequently

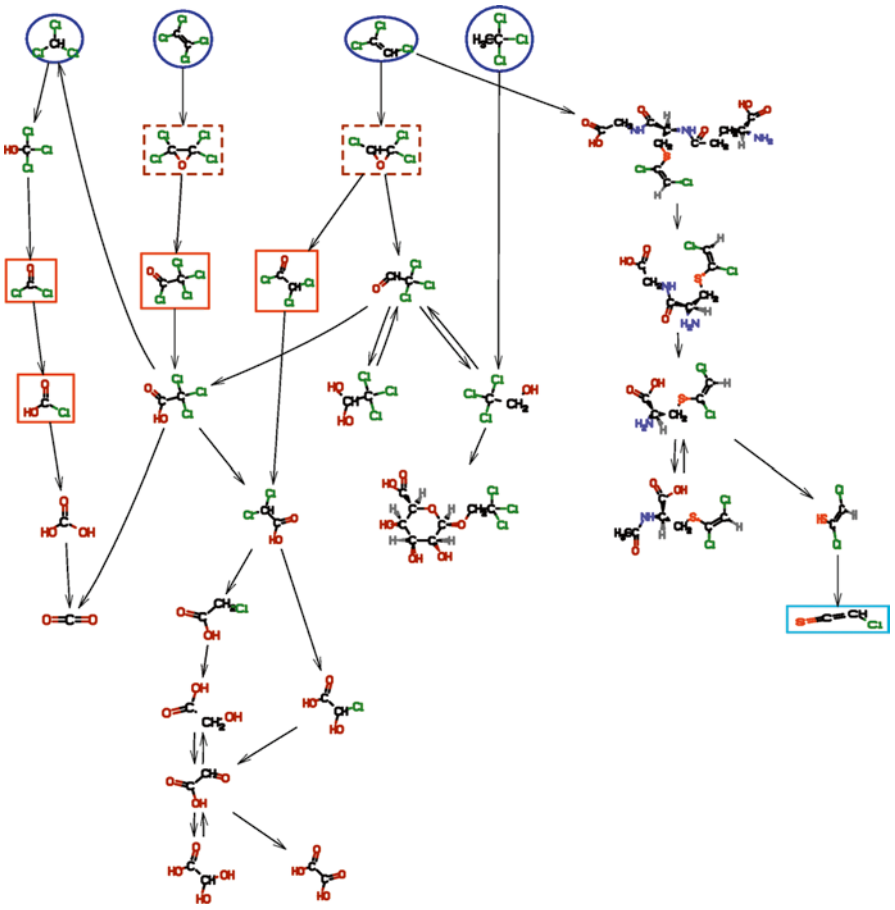

Fig. 11.3 BioTRaNS-generated biotransformation pathways for a mixture of trichloroethylene, PCE, methyl chloroform, and chloroform. Reactive metabolites are highlighted as follows: epoxides (*brown*, *box*, *dashed*); acid chlorides (*orange*, *box*, *solid*); thioketene (*turquoise*, *box*, *solid*); starting chemicals (*blue*, *ellipse*, *solid*)

involves an analysis of how xenobiotic-induced perturbations in gene and protein expression are linked to toxicological outcomes. The goal of systems biology modeling is to create holistic computational models of the functioning of the cell, multicellular systems, and ultimately the organism. These *in silico* models have the potential to elucidate linkages within and across the exposure-dose-effect continuum and may provide virtual test systems for evaluating the toxic responses of cells, tissues, and organisms.

Systems biology models and approaches for TCE are uncommon, though one such study was undertaken by Pleil (2009), who used a holistic approach and conceptual pathway model to begin to characterize and quantify the relationship between environmental exposures and human disease. By analyzing data obtained

in several exposure studies focused on TCE and methyl tertiary butyl ether, he determined the relative roles of contaminant concentration level, biological media (breath or blood), and the contaminant type on the variability of biomarker measurements. As a result of these analyses, Pleil found that the observed variance in biomarkers depended more on the variability in exposures than on interindividual differences in internal biological parameters, and suggested that in the longer term, such a systems biology approach has the potential to inform the assessment of susceptibility ranges along many relevant toxicological pathways.

11.7 Example: Modeling of TCE-induced Autoimmunity

Exposure to TCE has been found to trigger or exacerbate autoimmune responses and/or autoimmune diseases. Chemically-induced autoimmunity (Bigazzi 1988) is a complex process, involving, *inter alia*, exposure to the chemical, its absorption, distribution, metabolism, and elimination, interactions of the parent chemical and/or its metabolites with biological targets, epigenetic and other cellular alterations, and an immune response. Each of these elements, in itself, is an intricate process.

Although the role of TCE in inducing autoimmune disease has been qualitatively investigated and described in a number of references (Cooney and Gilbert 2012; Gilbert 2010; Gilbert et al. 2009; Cooper et al. 2009) including sections of this book, mathematical models describing the pathogenesis of TCE-induced autoimmunity are lacking. Mathematical modeling can be beneficial in a number of ways: for example, in testing hypotheses and gaining insights into the mechanism of the disease process, such as critical events leading to the disease, the time course of molecular and cellular processes during disease progression, the relative importance of processes and cell types involved. Moreover, once a model has been validated, its application may facilitate (a) reduced number of animals required in testing and more efficient experimental designs, (b) improved and personalized treatment regimens, as well as disease prevention, and (c) better prediction of the sequelae and/or prognosis of a disease. An excellent introduction to mathematical modeling of biological systems is presented by de Pillis and Radunskaya (2012).

Here, we illustrate an example of how to approach a first-generation model for TCE-induced autoimmunity (TAI). Before proceeding to develop a model, we should first identify the goals of the model, i.e., what questions do we want answered? For instance, suppose we wish to know if the magnitude of TCE-induced autoimmune hepatitis (AIH) could be estimated based on a quantitative measure of a biomarker, in a biological fluid such as blood or urine. In this case, the model should be focused on the liver (target organ), hepatitis (endpoint), and biomarkers in blood and urine (predictor variables). A literature search revealed no previous models of TCE-AIH, although other autoimmune diseases and processes have been modeled. Often, if the exact system of interest has not been modeled, models describing analogous or

related systems should be examined to consider whether the methodologies and approaches used for those systems can be adapted or serve as starting points.

Next, to develop this predictive model, an understanding of postulated and known mode-of-action of TCE-induced hepatitis would be necessary, as well as related aspects such as the ADME of TCE. If we are examining hepatitis of the liver, why is ADME important? It is because of what we wish the model to predict: here, the model must link biomarkers in blood and urine to pathologic features in the liver. Moreover, knowledge of the proposed pathogenetic mechanism of the disease indicates the importance of ADME: specifically, (a) TCE is transported via blood to the liver, metabolized, and eliminated, in a time-dependent fashion; (b) metabolites of TCE are believed to trigger or contribute to the disease onset, and (c) the biomarkers of interest are those in blood and urine.

The most straight-forward biomarkers would be TCE itself and its metabolites, in blood and urine. However, as hepatic concentrations are likely to more relevant than the concentrations in the blood, an important modeling aspect would be to relate blood or urine concentrations to those in the liver. This can be accomplished through the use of PBPK modeling (described above). Metabolism of TCE to reactive intermediates is mediated by enzymes, such as the cytochrome P450 2E1 enzyme, which show inter-individual variability and are chemically inducible. Adducts formed between reactive metabolites and biological targets, as well as perturbations to cellular processes (e.g., oxidative stress and consequent products like aldehydes) may contribute to the initiation, progression, and behavior of the autoimmune response, a process mediated by specific immune cell types and cell-signaling proteins such as cytokines. Further, TCE exposure has been associated with epigenetic alterations which may modulate the immune response. All of these processes involve temporal and spatial aspects. Thus, monitoring the appearance and disappearance of these specific liver events over time and relating them to biomarkers through mathematical models may lead to the discovery of biomarkers that can be used to better understand and predict disease progression. Further, a time-dependent evaluation of specific events within specific immune cell populations may also provide further insights. Thus, the experimental data should include "longitudinal" time points, collected over the course of the study.

A first-generation conceptual model for TCE-induced AIH is shown in Fig. 11.4. Note that the conceptual model does not include all known or proposed processes related to TCE-AIH pathogenesis; instead, only certain key steps are selected at this stage, in accordance to the principle of parsimony. To simulate the tissue distribution of TCE and other biomarkers, a PBPK model is coupled to the AIH model [step (0)]. Often, a PBPK model is linked with PD model to simulate the experimentally observed dynamic processes. Given a conceptual model, a mathematical model can be readily derived by writing an equation for each step. Specifically, the mathematical representation, corresponding to the beginning steps of the conceptual model in Fig. 11.4, is as follows:

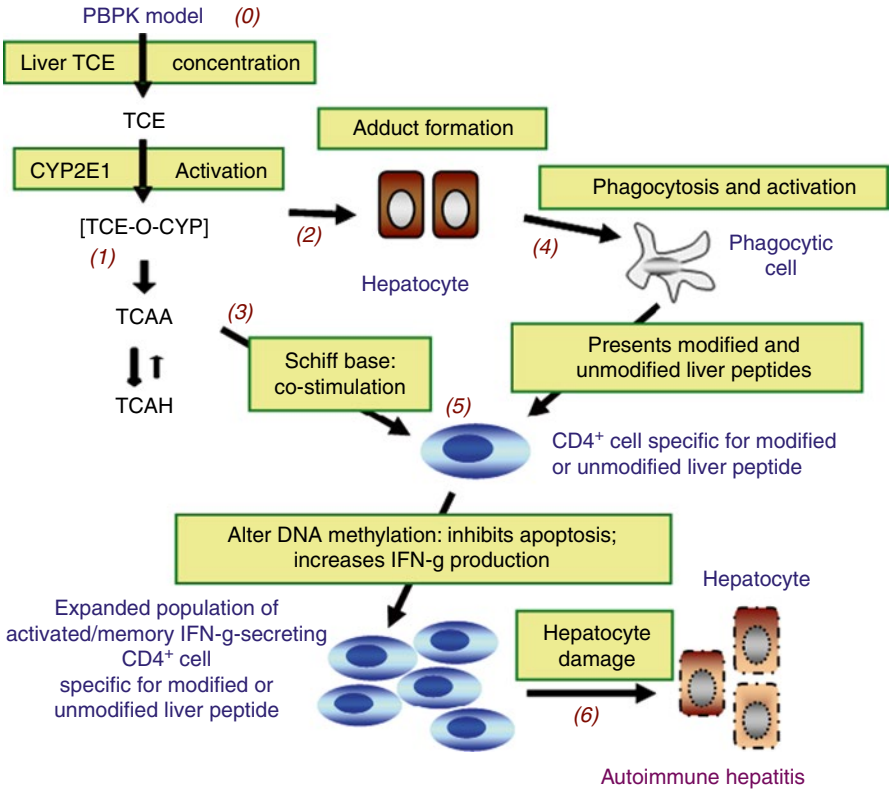

Fig. 11.4 Preliminary conceptual model TCE-induced autoimmune hepatitis

Step (0): PBPK Model: organ/tissue specific [TCE] over time

Step (1): $$R_{\text{met},i} = \frac{\mathrm{d}M_i}{\mathrm{d}t} = f_{i,\text{met}} \times \frac{V_{\max,\text{met}}[\text{TCE}]}{K_\text{m} + [\text{TCE}]}$$

Step (2): $$\frac{\mathrm{d}A_\text{add}}{\mathrm{d}t} = k_\text{add} R_{\text{met},a} - \frac{v_{\max,a} A_\text{add}}{K_{\text{rep},a} + A_\text{add}} + f_2$$

where

$R_{\text{met},i}$ = rate of TCE metabolism, where i = adducts or TCAH;

M_i = metabolite i;

t = time;

$f_{i,\text{met}}$ = fraction of metabolites that are of type i;

$V_{\max,\text{met}}$ = maximum rate of formation of metabolites;

K_m = Michaelis constant for metabolite formation;

[TCE] = TCE concentration at the site of metabolism;

A_{add} = amount of adduct formed;

k_{add} = rate constant for adduct formation;

$v_{max,a}$ = maximum repair capacity due to damage by adduct formation;

$K_{rep,a}$ = "half-saturation constant" for repair capacity; and

f_2 = addition term to be added later during model refinement.

Although TCE and its metabolites are the most straight-forward biomarkers, other biomarkers may better correlate TCE-AIH disease pathology. The selection of the biomarkers to be examined should be based on knowledge of the pathogenetic mechanism. The experimental work required to identify predictive biomarkers could be a major effort.

Finally, once a first generation model has been developed, the model can be further enhanced to allow for the investigation of a variety of other relevant research questions, such as the details of the mechanism of disease induction, the contribution of different immune cell types, and genetic predisposition to TCE-AIH, just to list a few potential applications.

Acknowledgements The authors thank Dr. Arthur N. Mayeno for his contribution to the materials contained in this chapter.

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