state concentrations of chemicals in blood and tissues can be adequately deter-
mained using algebraic equations that use fewer parameters than full-blowm
PBPK models. The purpose of this study was to develop a simple algebraic
approach for conducting sensitivity and variability analyses in human PBPK
models of volatile organic chemicals (VOCs). Since the human models are
used to simulate lifetime exposures, algebraic equations instead of full-blowm
PBPK models were used to obtain essentially the same results. Using the alge-
braic equation, the sensitivity of steady-state arterial blood concentration [C_an
= 1/(P_b + Q_h * E)] where P_b = blood:air partition coefficient, Q_h = fraction of
blood flow to the liver and E = hepatic extraction ratio) of 17 volatile organ-
ic chemicals (VOCs) was determined for unit change in the numerical values of
E, P_b and Q_h. The percent change in C_an for 1% change in P_b, E or Q_h ranged
from 0.04 to 0.99, 0.01 to 0.97, and 0.01 to 0.97, respectively. Given a ±5 % and
22 % variability of P_b and Q_h in a population, C_an would vary by ±0.5-14% and
±0.27-26%, respectively. A 50% increase in E would lead to 0.6-29% decrease
of C_an while a 50% decrease in E resulted in 0.6-92% increase in C_an. This algebraic
approach can provide the extreme values of PK endpoints (e.g., C_an) for a given range of variability of input parameters in a population. Distributions of parameter values, if available, can also be
used with this algorithm for assessing the probabilistic nature of the outcome.

424 IMPROVING THE RELIABILITY OF PARAMETERS IN PBTK
MODELS USING MARKOV CHAIN MONTE CARLO
SIMULATIONS.
F. Jonsson and G. Johnson. National Institute for Working Life, Stockholm,
Sweden.
The kinetics of volatile substances can be described with the aid of physio-
logically based toxicokinetic (PBTK) models. However, such modeling is
often performed without assessing the reliability of the parameters and their
variability in the population. The aim of this study was to address these issues
within a population PBTK framework using Markov chain Monte Carlo
(MCMC) simulations. The MCMC method creates parameter estimates in the
shape of distributions, incorporating existing data on the parameter distribu-
tions in the population. In a previous study (Jonsson, Scand J Work Environ
Health. 8 (1982), 43-55), 6 male volunteers were exposed to toluene vapor for
two hours at 80 ppm during various levels of exercise. Extensive physiologi-
cal and kinetic data, such as toluene in arterial blood, subcutaneous adipose
tissue and end-exhaled air, were collected up to one week postexposure. Thus,
the Carlsson data were deemed suitable for this study. The kinetic data were
fit to a published PBTK model for toluene (Pierce et al., Toxicol Appl
Pharmacol 139 (1995), 49-61). The results suggest that a separate compart-
ment for peripheral fat should be added to the model from Pierce et al. in
order to describe the concentration-time profile in subcutaneous fat correctly.
Furthermore, by using the information supplied by the experimental data it is
possible to improve the reliability of the distributions of the fat-related phys-
iological parameters. (The study was financially supported by the Swedish
Council for Work Life Research.)

425 APPLICATION AND USE OF DOSE ESTIMATING EXPOSURE
MODEL (DEEM) FOR ROUTE TO ROUTE DOSE
COMPARISONS AFTER EXPOSURE TO
TRICHLOROETHYLENE (TCE).
C. S. Scott, J. N. Blancato, J. W. Power and J. W. Fisher. USEPA, Washing-
ton DC, USEPA, Las Vegas, NV, Anteon Corporation, Las Vegas, NV and 'For the Anteon
Corporation, Las Vegas, NV.
Route to route extrapolations are a crucial step in many risk assessments.
Often the doses which result in toxicological end-points in one route must be
compared with doses resulting from typical environmental exposures by
another route. In this case we used EPA's Dose Estimating Exposure Model
(DEEM) to examine the route comparisons of different measures of internal
dose after exposure to TCE. DEEM is a physiologically based model archi-
tecture for estimating internal tissue doses resulting from actual or simulated
exposures. Because of different kinetic rates in the body not each possible
measure of dose has the same quantitative relationship with exposure.
Modeling shows that for different choices of internal dose the "equivalent"
exposures are different. For example, we first chose the dose of interest to be
the area under the curve (AUC) of the metabolite, trichloroacetic acid (TCA).
In this case and with this model set-up an 8-hour 30 ppm exposure via inhala-
tion was equivalent to drinking water intake of 50mg per day. For other mea-
sures of dose the point of equivalent exposure is far different. Thus, informa-
tion about the mode of action and selection of internal dose is crucial before
route to route extrapolations can be rationally made. (NOTICE: The U.S.
Environmental Protection Agency (EPA), through its Office of Research and
Development, funded this research and approved this abstract as a basis for
an oral presentation. The actual presentation has not been peer reviewed by the
EPA. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.)