REGULATORY TOXICOLOGY AND PHARMACOLOGY **26,** 257–270 (1997)
ARTICLE NO. RT971168

Combining Physiologically Based Pharmacokinetic Modeling with Monte Carlo Simulation to Derive an Acute Inhalation Guidance Value for Trichloroethylene[1]

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Received May 14, 1997

Using the Monte Carlo method and physiologically based pharmacokinetic modeling, an occupational inhalation exposure to trichloroethylene consisting of 7 h of exposure per day for 5 days was simulated in populations of men and women of 5000 individuals each. The endpoint of concern for occupational exposure was drowsiness. The toxicologic condition leading to drowsiness was assumed to be high levels of both trichloroethanol and trichloroethylene. Therefore, the output of the simulation or dose metric was the maximum value of the sum of the concentration of trichloroethylene in blood and the concentration of trichloroethanol within its volume of distribution occurring within 1 week of exposure. The distributions of the dose metric in the simulated populations were lognormal. To protect 99% of a worker population, a concentration of 30 ppm over a 7-h period of the work day should not be exceeded. Subjecting a susceptible individual (the 99th percentile of the dose metric) to 200 ppm (the ACGIH short-term exposure limit or STEL) for 15 min twice a day over a work week necessitates a 2.5-h rest in fresh air following the STEL exposure to allow the blood concentrations of trichloroethylene and trichloroethanol to drop to levels that would not cause drowsiness. Both the OSHA PEL and the ACGIH TLV are greater than the value of 30 ppm derived here. As well as suggesting a new occupational guidance value, this study provides an example of this method of guidance value derivation.

INTRODUCTION

The function of guidance values or safe exposure limits for hazardous chemicals is protection of human health. This study is an attempt to quantify human variability and to use this measure of variability to derive a safe exposure limit or guidance value for inhalation of trichloroethylene (TRI) in an occupational setting.

Ideally, guidance values, such as threshold limit values (TLVs) from the American Congress of Government Industrial Hygienists (ACGIH), permissible exposure levels (PELs) from the Occupational Safety and Health Administration (OSHA), and acute inhalation minimal risk levels (MRLs) from the Agency for Toxic Substances and Disease Registry (ATSDR), serve to protect the target human population and also permit cost-effective use of a chemical within regulatory constraints.

Regulatory agencies have begun to use physiologically based pharmacokinetic (PBPK) modeling to determine guidance values for several volatile organic chemicals (Clewell *et al.*, 1995) and methyl mercury (USEPA, 1997). The most widely known use of such a model is the integrated exposure uptake/biokinetic (IEUBK) model for lead exposure in children that is used by the Environmental Protection Agency (USEPA, 1994).

A few PBPK modeling studies have attempted to account for human variability including body build and pulmonary ventilation (Fiserova-Bergerova *et al.*, 1980), amount of body fat (Fisher *et al.*, 1997), and fitness (Pierce *et al.*, 1996). However, these studies did not attempt to derive guidance values.

Variability in human response can be treated effectively using probabilistic methods. This study uses both PBPK modeling and the Monte Carlo method to derive a guidance value or safe limit for exposure to TRI in the work place. The emphasis here is on the variability of human responses. Hence, all probabilistic parameters used in the model are based on actual human data. The endpoint of fatigue or drowsiness was chosen because it can be an important hazard in occupational settings. Drowsiness in response to trichloroethylene exposure may be due to the parent compound (Amdur *et al.*, 1993) or to trichloroethanol (TCOH), a metabolite with known sedative properties (Butler, 1948), or both

[1] This manuscript and the information herein were developed by the author in his private capacity. No official support or endorsement by the Environmental Protection Agency or any other agency of the U.S. Government is intended or should be inferred.

0273-2300/97 $25.00

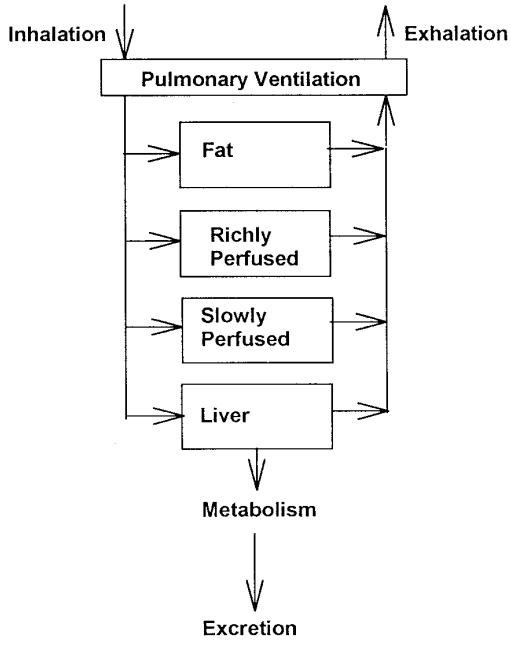

FIG. 1. Schematic diagram of the PBPK model used in this simulation. The model is quite simple with only four compartments interconnected by their blood supply. The only portal of entry for trichloroethylene is the lungs, and ingestion was specifically excluded.

compounds. The variability of the toxicodynamic response, i.e., that of the brain, has not been explicitly included in the model but is believed to be insignificant relative to toxicokinetic variability. The guidance values derived here are compared to those currently used for regulating the workplace. The occupational guidance value for TRI derived here is neither endorsed nor supported by EPA or any other agency of the U.S. government.

METHODS

PBPK Model

The model was similar to those used earlier in an examination of the possible carcinogenic effects of TRI (Fisher *et al.*, 1991; Fisher and Allen, 1993; Allen and Fisher, 1993; Cronin *et al.*, 1995). Tissue mass balance was achieved with a four-compartment model including a liver compartment, a fat compartment, a richly perfused compartment, and a slowly perfused compartment (Fig. 1). Because of the need to account quantitatively for TCOH, the model's depiction of TRI metabolism is somewhat more complex than earlier models (Fig. 2) but, nonetheless, more simple both in terms of number of compartments and metabolism than a model presently being considered for regulation of carcinogenic effects of TRI (Clewell *et al.*, 1995). Model parameter names, calculation methods, and values are presented in Tables 1–3.

The dose regimen applied to the model was the occupational exposure used in human experiments by Stewart *et al.* (1970). Individuals were exposed to 200 ppm TRI in air for 3 h followed by 1-h break and then for an additional 4 h. This exposure was repeated for 5 days.

Metabolism

Trichlorooethylene is metabolized by cytochrome P450 2EI (CYP2EI) to chloral hydrate (CH) (Lipscomb *et al.*, 1997). The chloral hydrate is rapidly oxidized to trichloroacetic acid (TCA) or reduced to TCOH (Lipscomb *et al.*, 1996). TCOH is the metabolite of CH responsible for its sedative effects (Butler, 1948; Sellers *et al.*, 1978). TCOH may be converted to TCA or conjugated with glucuronic acid to form trichloroethanol-glucuronide (TCOG). TCA and TCOG are excreted in the urine (Fig. 2). Minor metabolites include dichloroacetic acid, monochloroacetic acid, and oxalic acid (Lipscomb *et al.*, 1996).

CH is not explicitly represented in the model because its conversion to either TCA or TCOH is rapid compared to its formation from TRI. The ratio of the Michaelis-Menten constants, V_{max}/K_m, is approximately equal to the first order rate constant of an enzymatic reaction (Reitz *et al.*, 1996). These rate constants, calculated from published values, suggest a 20- to 1000-fold difference in the reaction rates (Lipscomb *et al.*, 1996, 1997) and supports the rate-limiting step as oxidation of TRI to CH by CYP2EI rather than subsequent reactions of CH. A smaller portion (PO) of the TRI is assumed to be oxidized to TCA, and the larger portion remaining is reduced to TCOH (Marshall and Owens, 1954; Barton *et al.*, 1996; Fig. 2). TCOH is oxidized to TCA or conjugated to form TCOG; both these reactions

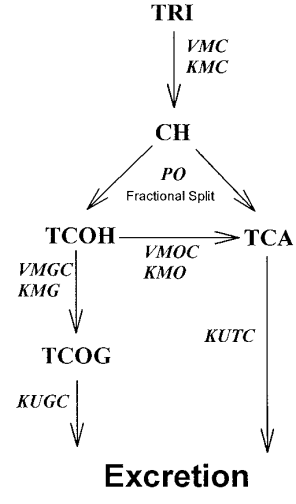

FIG. 2. Schematic diagram of trichloroethylene metabolism in the PBPK model. The metabolic parameters supplied to the model are shown in italics next to the appropriate arrows.

TABLE 1
Sources of Probabilistic Parameter Distributions

Parameter	Source
Pulmonary, cardiac, and tissue flows	
Pulmonary ventilation (QPC) (L/kg/h)	ILSI, 1994; ICRP, 1975
Cardiac output multiplier for QPC (unitless) (QCC = VP_Ratio * QPC)	Green, 1987
Liver blood flow (QLC) (%)	Thomas *et al.*, 1996
Fat blood flow (QFC) (%)	Williams and Leggett, 1989; Thomas *et al.*, 1996
Slowly perfused blood flow (QSC) (%)	Thomas *et al.*, 1996
Richly perfused blood flow (QRC) (%)	Thomas *et al.*, 1996
Body weight and tissue volumes (fraction of body weight/volume)	
Body weight (BW) (kg)	Stoudt *et al.*, 1960
Liver volume (VLC) (%)	Thomas *et al.*, 1996
Fat volume (VFC) (%)	Males: ILSI, 1994 Females: Rutishauer *et al.*, 1995
Richly perfused volume (VRC) (%)	Thomas *et al.*, 1996
Slowly perfused volume (VSPC) (%)	Thomas *et al.*, 1996
Partition coefficients (unitless)	
Blood/air (PB)	M. L. Gargas, personal communication, 1996; Gargas *et al.*, 1989
Fat/air (PFA)	
Liver/air (PLA)	
Richly perfused/air (PRA)	
Slowly perfused/air (PSA)	
Metabolic parameters	
Maximum oxidation rate of TRI by CYP2EI (VMC) (pmol/mg protein/min)	Lipscomb *et al.*, 1997
Substrate affinity of CYP2EI for TRI (KMC) (μmol)	Lipscomb *et al.*, 1997
Portion CH Oxidized to TCA (PO) (%)	Marshall and Owens, 1954; Barton *et al.*, 1996

Note. Literature sources of the parameter values used in the Monte Carlo simulation. The values for the metabolic constants for TCOH oxidation to TCA, TCOH glucuronidation, and the urinary excretion constants for TCA and TCOG were determined by parameter optimization and are not included in this table.

were assumed to occur by saturable enzymatic processes. Between 5 and 47% of CH is metabolized to TCA. (Marshall and Owens, 1954). DCA or other minor metabolites were not explicitly modeled because of their rapid clearance (Dekant *et al.*, 1984, 1986).

TCA, TCOH, and TCOG were modeled within similar volumes of distribution calculated from the body weight. The volume of distribution for each was assumed to be 0.65 multiplied by the body weight (Clewell *et al.*, 1995). All TCA and TCOG present in their respective volumes of distribution was available for urinary excretion via first order processes. Both urinary and fecal excretion of TCOG occur in humans with fecal excretion comprising less than 5% (Müller *et al.*, 1974). Excretion of TCOG in the model should be considered as the algebraic sum of urinary and biliary/fecal excretion and reabsorption from the intestine.

Modeling

SCoP (Simulation Control Program from Simulation Resources, Inc., Berrien Springs, MI) was used in batch mode to conduct the simulations (Simulation Resources, Inc., 1996). Source code for the model is available from the author.

For each run, the code checked the mass balance of TRI and its metabolites, and if the mass balance of either the parent or the metabolites departed from zero, the run was discarded. The model was performed successfully 5000 times each for men and women.

Monte Carlo Methodology and Parameter Selection

Distributions of physiological parameters were taken from ILSI (1994), Thomas *et al.*, (1996a), and several other sources. Parameter references are given in Table 1.

The 25 parameters in the model could be divided into four categories: volumes, flows, partition coefficients, and metabolic/kinetic constants. Parameters were assumed to follow normal, lognormal, or uniform distributions. Parameters for normal and lognormal distributions were determined by established methods using random numbers (Thomas *et al.*, 1996b). Random numbers were generated with Pascal code (Press *et al.*, 1986). The code was capable of producing more than 5000 random decimals between 0 and 1 that occurred in a statistically uniform distribution. Crystal Ball software (Version 3.0, Decisioneering, Inc.) was used to generate correlated uniform distributions of metabolic parameters (see below). Selected other parameters were correlated based on their dependence on body weight. The parameter selection program, including the random number generator, was written in Turbo Pascal Version 5.0 (Borland, Inc., Scotts Valley, CA) and is available from the author.

For compartmental volumes and flows, values for three of four parameters were determined by probabilistic methods and the fourth by subtraction (Thomas *et al.*, 1996a; Table 2). Covariance between cardiac output and pulmonary ventilation was treated by calculating ventilation and then setting cardiac output using a probabilistic estimate of their ratio (VP_Ratio) (Green, 1987; Tables 1 and 2).

Partition coefficients were taken from Gargas *et al.* (1989) and modified after discussions with Dr. Gargas (Gargas, personal communication; Table 2).

V_{max} and K_m for TRI oxidation by cytochrome P450 2EI were bootstrapped from the data obtained from human liver samples (Lipscomb *et al.*, 1997). Uniform distributions were used for other metabolic and urinary excretion parameters. The ranges for these distributions were determined by parameter optimization. Al-

TABLE 2
Probabilistic Parameter Distributions and Values

Parameter name	Parameter	Distribution	Men		Women	
			Mean	STD	Mean	STD
	Pulmonary, cardiac, and tissue flows					
QPC	Pulmonary ventilation (L/kg/h)	Normal	15.0	4.2	15.0	4.2
VP_Ratio	Multiplier for QPC to find QCC (unitless) (QCC = VP_Ratio * QPC)	Lognormal	1.0	0.65	1.0	0.65
QCC	Cardiac output (L/kg/h) (QCC = VP_Ratio * QPC)					
QLC	Liver blood flow (%)	Normal	0.25	0.07	0.27	0.076
QFC	Fat blood flow (%)	Normal	0.05	0.013	0.085	0.016
QSC	Slowly perfused blood flow (%)	Normal	0.19	0.086	0.19	0.086
QRC	Richly perfused blood flow (%)		Calculated as remaining fraction			
	Body weight and tissue volumes (fraction of body weight/volume)					
BW	Body weight (kg)	Normal	71.7	10.0	58.0	8.6
VLC	Liver volume (%)	Normal	0.026	0.0052	0.026	0.0052
VFC	Fat volume (%)	Normal	0.136	0.053	0.231	0.086
VRC	Richly perfused volume (%)	Normal	0.06	0.0114	0.06	0.0114
VSC	Slowly perfused volume (%)		Calculated as remaining fraction			
	Partition coefficients (unitless)					
PB	Blood/air	Normal	7.97	0.6	Same for females.	
PFA	Fat/air	Normal	554	36.4	Blood/tissue partition coefficients were calculated as the ratio between the blood/air PC and the tissue/air PC.	
PLA	Liver/air	Normal	27.2	10.2		
PRA	Richly perfused/air	Normal	27.2	10.2		
PSA	Slowly perfused/air	Normal	10.2	6.6		

Note. Values of the probabilistic parameters used in the Monte Carlo simulations. For normal distributions, the set of parameters was calculated using the means and standard deviations given in the table. For the lognormal distributions, the means and standard deviations are in fact the geometric means and geometric standard deviations, and the parameters were calculated accordingly.

though these data could be fit to normal or lognormal distributions (Table 5), uniform distributions were chosen for the PBPK model because they tend to emphasize the tails of the output distribution (Lipton *et al.*, 1995) and the high-end tail of this distribution is of greatest interest for guidance value derivation.

Determination and Selection of Metabolic Parameters for TRI

The Michaelis–Menten parameters for the oxidation of TRI to CH by CYP2EI have been measured in 23 individual human liver samples (Lipscomb *et al.*, 1997). A bootstrap procedure was used to select from these 23 values for VMC and KMC (Table 3). Simply, 23 equal ranges were chosen between 0 and 1, and each of the 23 sets of VMC and KMC was assigned to a range. A random number was generated, and the range in which it fell indicated the specific parameters.

A variation of the method of Reitz *et al.* (1996) was used to convert the *in vitro* data to the appropriate values for use in the model. The ratio of V_{max} *in vivo* to that *in vitro* was determined by optimization to be 2.0 (Eq. (1)). The *in vitro* data of Lipscomb *et al.* (1997) were converted to the units of milligrams of TRI per kilogram of liver per hour for VMC and milligrams per liter for KMC as follows:

$$\text{VMC: } A \frac{\text{pmol}}{\text{mg protein} \cdot \text{min}} \cdot 12800 \frac{\text{mg protein}}{\text{kg liver}} \cdot 1.315\text{E} - 07 \frac{\text{mg TRI}}{\text{pmol}} \cdot 60 \frac{\text{min}}{\text{h}} \cdot 2.0 = B \frac{\text{mg TRI}}{\text{kg liver} \cdot \text{h}}, \quad (1)$$

where A is the value supplied to model and B is the value used in calculation.

$$\text{KMC: } A \frac{\mu\text{mol}}{\text{L}} \cdot 0.1315 \frac{\text{mg TRI}}{\mu\text{mol}} = \text{B} \frac{\text{mg TRI}}{\text{L}}, \quad (2)$$

where A is the value supplied to model and B is the value used in calculation.

TABLE 3
Metabolic Parameters

Parameter name	Parameter	Distribution	Men and women	
			Range	Source
PO	Portion of CH oxidized to TCA (%)	Normal	Mean, 25.0 STD, 9.0	Truncated at 5 and 47%
VMC	V_{max} for TRI oxidation by cytochrome P450 2EI (mg/kg-h)	Bootstrap		Lipscomb *et al.*, 1997
KMC	K_m or substrate affinity of cytochrome P450 2EI for TRI (mg/L)	Bootstrap		Lipscomb *et al.*, 1997
VMOC	V_{max} for oxidation of TCOH to TCA (mg/kg-h)	Uniform	0.12–95.2	Optimization (see text)
KMO	K_m or substrate affinity for oxidation of TCOH to TCA (mg/L)	Uniform	2.38–803.4	Optimization (see text)
VMGC	V_{max} for glucuronidation of TCOH to TCOG (mg/kg-h)	Uniform	0.1–12.0	Optimization (see text)
KMG	K_m or substrate affinity for glucuronidation of TCOH to TCOG (mg/L)	Uniform	1.27–178.9	Optimization (see text)
KUGC	First order excretion constant for TCOG (/h)	Uniform	0.044–11.5	Optimization (see text)
KUTC	First order excretion constant for TCA (/h)	Uniform	0.00001–0.3	Optimization (see text)

Note. Parameter list, distribution types, and values for the metabolic parameters used in the model. Figure 2 shows a schematic diagram of the role of these parameters in TRI metabolism.

Determination of Metabolic Parameters for TCOH and TCA by Optimization

Oxidation of TCOH to TCA and TCOH conjugation to glucuronic acid were assumed to occur by Michaelis–Menten kinetics, and excretion of both TCA and TCOG was assumed to be first order (Fig. 2).

Michaelis–Menten parameters (Table 3) for the oxidation of TCOH to TCA (VMOC and KMO), the glucuronidation of TCOH to TCOG (VMGC and KMG), and the urinary excretion constants for TCA (KUTC) and TCOG (KUGC) were determined by optimization of these parameters to three data sets: (1) the appearance of TCOG and TCA in plasma after ingestion of CH or the sodium salt of TCOH (Sellers *et al.*, 1978); (2) the appearance of TCA and TCOG in urine after inhalation of TRI (Stewart *et al.*, 1970); and (3) the appearance of these same metabolites in urine following TRI inhalation from Sato *et al.* (1977). Ranges for these six parameters (VMOC, KMO, VMGC, KMG, KUGC, and KUTC) from these three optimizations were used as the high and low values of uniform distributions used in the Monte Carlo simulation (Tables 3 and 4).

The starting parameters for the fits were taken from Clewell *et al.* (1995). To ensure that all fits were robust and converged to the same set of numbers, starting parameters were varied and the fits performed several times.

Parameter optimization based on the data of Sellers et al. (1978). CH and TCOH were administered to hospitalized patients without liver disease. Blood concentrations of TCOH, TCA, and TCOG were determined (Sellers *et al.*, 1978). Data for plasma concentrations of TCOH and TCA were obtained from Fig. 1 of Sellers *et al.* (1978). To determine ranges for the maximal enzyme rates, substrate affinities, and the two urinary rate constants, a reduced model (available from the author) was developed that included only the metabolism and excretion of TCOH. The range for TCOH and TCA blood concentrations was also assumed to lie between the mean minus 0.5 standard deviations and the mean plus 2 standard deviations. Blood concentrations less than 0.5 standard deviations below the mean were not used because in almost all cases, these were negative numbers.

TCOH blood concentrations were supplied to the reduced model using the generalized forcing function of SCoP (Simulation Resources, Inc., 1996). Forcing functions were generated for the low range, the mean, and the high range of TCOH in blood. The low range, the mean, and the high range of the TCOH blood concentrations were each fitted to the low range, mean, and high range of the TCA blood concentrations.

Since each of three data sets for TCOH concentrations was fit to each of three data sets (low, mean, high) for TCA concentrations, once for CH administration and again for TCOH administration, this procedure yielded 18 values for each parameter.

Parameter optimization based on the data of Stewart et al. (1970). The ranges of these six parameters were also estimated by fitting the full TRI model to the appearance of TCA and TCOG in the urine (Table II in Stewart *et al.*, 1970). The six parameters were fit to the high and low ends of the range and the mean of the urinary metabolite concentrations. Fits were performed for the high, low, and mean data using each of the 23 values of V_{max} and K_m for TRI oxidation by CYP2EI (Lipscomb *et al.*, 1997). In this way, a data set of 69 values for each of the six parameters for the appearance of TCA in the urine was determined, and another data set of 69 values for the appearance of TCOG in the urine was also determined.

TABLE 4
Ranges of Optimized Metabolic Parameters

Study or grouping	Parameters			
	Low value	High value	Low value	High value
	VMOC		KMO	
Overall	0.12	95.2	2.38	803.4
Sellers *et al.* (1978)	0.12	2.35	55.1	650.5
Stewart *et al.* (1970), TCA in urine	0.77	57.25	2.38	727.14
Stewart *et al.* (1970), TCOG in urine	1.4	35.6	150.0	760.7
Sato *et al.* (1977), TCA in urine	1.25	60.26	162.2	803.4
Sato *et al.* (1977), TCOG in urine	1.99	95.23	9.49	687.7
	VMGC		KMG	
Overall	0.1	12.0	1.27	178.9
Sellers *et al.* (1978)	0.74	6.78	13.7	80.9
Stewart *et al.* (1970), TCA in urine	0.1	2.17	5.12	178.9
Stewart *et al.* (1970), TCOG in urine	0.71	5.18	9.94	44.24
Sato *et al.* (1977), TCA in urine	1.1	12.0	5.42	45.7
Sato *et al.* (1977), TCOG in urine	0.82	10.27	1.27	72.0
	KUGC		KUTC	
Overall	0.044	11.5	0.00001	0.3
Sellers *et al.* (1978)	0.87	3.6	0.00001	0.3
Stewart *et al.* (1970), TCA in urine	0.36	8.64	0.023	0.066
Stewart *et al.* (1970), TCOG in urine	0.044	0.6	0.00001	0.001
Sato *et al.* (1977), TCA in urine	0.27	7.96	0.012	0.022
Sato *et al.* (1977), TCOG in urine	0.175	11.5	0.02	0.027

Note. Ranges of optimized parameters used for Monte Carlo parameter generation for kinetic constants related to TCOH metabolism and excretion. The ranges were obtained by fitting the model to five different data sets from three human studies. There is considerable overlap among the parameter ranges determined from the various data sets. See text for details of the optimization.

Parameter optimization based on the data of Sato et al. (1977). The ranges of the six parameters were estimated by fitting the TRI model to the appearance of TCA and TCOG in the urine of four Japanese men (Table 3 in Sato *et al.*, 1977). The low and high values for the metabolites in urine were assumed to be the mean minus 0.5 standard deviations and the mean plus 2 standard deviations, respectively. The generation of fitted parameters for the appearance of both metabolites in the urine was performed 23 times for each metabolite as described above, again yielding 69 values for fits to TCA in urine and 69 values for fits to TCOG in urine.

Criteria for Assuming Correlations between the Optimized Parameters

Correlations between these six optimized metabolic parameter distributions were determined for the combined overall data (all parameter estimations from Sellers *et al.* (1978), Stewart *et al.* (1970), and Sato *et al.* (1977)), the fits resulting from each study and the fits based on either TCA or TCOG excretion using the Spearman rank correlation procedure. If (1) the overall data and (2) two of three studies or (3) fits based on TCA excretion and fits based on TCOG excretion indicated a statistically significant correlation was present, then a rank correlation coefficient was determined for the overall data set and used during Monte Carlo parameter generation.

Choice of Dose Metric

A dose metric is considered an internal measure of toxicologic or pharmacologic exposure. The dose metric for a particular exposure is related by physiological principles to the occurrence of an adverse effect.

For acute exposures, the major effect of TRI is on the nervous system—headaches, fatigue, and drowsiness (Salvini *et al.*, 1971; Stewart *et al.*, 1970, 1974).

Stewart *et al.* (1970) observed mild fatigue, sleepiness, and a subjective observation of increased difficulty in simple neurobehavioral tasks in volunteers exposed to 200 ppm trichloroethylene in a 7 h/day occupational exposure conducted over 5 days. Fifty percent of the subjects reported increased difficulty with neurobehavioral tests; all of the subjects reports feeling "fatigued"; and 60% reported feeling "sleepy" during the exposure.

TRI would exert a generalized solvent effect on the brain (Amdur *et al.*, 1993), potentially causing sleepiness, and TCOH is a known sedative (Butler, 1948; Sellers *et al.*, 1978). Although there was no explicit compartment for the brain in the model, TRI and

TCOH should rapidly equilibrate with richly perfused lipid-rich brain tissue. Hence, the sum of arterial blood concentration of TRI and the concentration of TCOH in its volume of distribution was considered the most appropriate dose metric for sleepiness.

The neurobehavioral deficits reported in Stewart *et al.* (1970) are likely physicochemical solvent effects on the neural membranes needed for proper brain functioning (Amdur *et al.*, 1993). TRI has been reported to produce a direct toxic effect on the lipid composition of the myelin sheath around axons (Kyrkland *et al.*, 1983), but whether this effect functions to produce drowsiness is unknown.

In each of the Monte Carlo simulations, the maximum value of the dose metric ([TRI] in blood + [TCOH] in its volume of distribution) was saved. [TCOH] comprised the majority of the dose metric value—greater than 90% in all cases—because metabolic processes rapidly converted any inhaled TRI preferentially to TCOH.

During a single simulation, the sum of [TRI] and [TCOH] in blood would reach its maximum value at the end or shortly after the end of a day's exposure, usually on the fifth exposure day. The maximum value of the sum of [TRI] and [TCOH] in blood was saved by the model but the time at which this value occurred was not saved. Thus, the dose metric for each simulation and the distribution of dose metrics resulting from the Monte Carlo simulations are considered independent of time.

Sensitivity Analysis

Sensitivity of the dose metric to the individual model parameters was examined using the Spearman rank correlation coefficient and the relative partial sum of squares multiple regression technique (Rose *et al.*, 1991) to ascertain the relative contribution of each to the variation in the dose metric.

Parameter Analysis within the Upper 5% of the Distributions of the Dose Metric

It is generally preferable to derive a guidance value protective of 100% of the potentially affected population. In this study, there was a greater arithmetic range of dose metric values between the 95th percentile and the 100th percentile than between the 40th and 95th percentiles for both males and females. The question was posed whether some or all of these simulated individuals between the 95th and 100th percentiles are composed of realistic combinations of parameters. If these high-end individuals are "realistic," it would be prudent to protect 100% of the simulated individuals.

The simulated individuals within the top 5% range of the dose metric were classified as unrealistic based on three criteria: (1) if the ratio between cardiac output and pulmonary ventilation (QCC/QPC) was greater than 2 or less than 0.5; (2) if the amount of body fat (VFC) was less than 5%; and (3) if blood flow to the liver (VLC) was less than 15%. A mismatch between cardiac output and pulmonary ventilation often reflects underlying disease that should not be present in healthy workers (Green, 1987). Reduction in hepatic blood flow often indicates disease such as cirrhosis (Amdur *et al.*, 1993). Five percent body fat can be considered a lower bound for both men and women (Rutishauer *et al.*, 1995; ILSI, 1994).

The distributions for these parameters were not truncated during parameter generation. At the outset of the Monte Carlo simulations, it was felt that the simulated population should not be arbitrarily limited in its variability. However, a safe exposure limit or guidance value should be based on realistic estimates.

Hence, 41 of the simulated males and 60 of the simulated females were eliminated from the top 5% of the Monte Carlo sample. Therefore, it was decided to derive a guidance value to protect the individual at the 99th percentile and below; i.e. elimination of approximately 50 individuals would be a reduction of 1% in a sample of 5000.

RESULTS

Metabolic Parameters for TCOH Metabolism

The ranges of the six parameters (VMOC, KMO, VMGC, KMG, KUGC, and KUTC) based on the various data sets are shown in Table 4. There was overlap between the ranges determined using data from the three studies discussed under Methods. There is considerable variability between the three studies used because of the variability in excretion of TRI metabolites. A recent study of TRI inhalation also showed considerable variability of urinary metabolites (Fisher *et al.*, 1997).

No statistics were used to compare the values obtained from each study because the data set from each was too small to generate a recognizable distribution. The values for these same parameters used by Clewell *et al.* (1995) were within the ranges determined here. Distributions were determined for the combined data sets for these parameters from all three studies (Table 5). These distributions were not used in the PBPK model—uniform distributions were used for these metabolic parameters.

In the overall optimized data, VMOC is positively correlated with VMGC (VMOC-VMGC: $r_s = 0.407$, $P < 0.05$) and negatively correlated with KMG (VMOC-KMG: $r_s = -0.234$, $P < 0.05$) and KUGC (VMOC-KUGC: $r_s = -0.309$, $P < 0.05$). No other parameters were correlated under the criteria presented under Methods.

Validation of the Model

Based on the values of the dose metric, individuals from the distributions of 5000 each of men and women

TABLE 5
Distributions of the Fitted Parameters Determined from Combined Data

Parameter	Distribution type	Mean	Standard deviation
VMOC	Lognormal	25.5	58.8
KMO	Normal	301.1	162.2
VMGC	Lognormal	3.7	3.2
KMG	Lognormal	29.1	20.5
KUGC	Lognormal	1.58	4.7
KUTC	Lognormal	0.04	0.033

Note. Distributions of the optimized metabolic parameters obtained from combining the values obtained from all three studies (Sellers *et al.* 1978; Stewart *et al.* 1970; Sato *et al.* 1977) ($n > 250$). Uniform distributions were used in the parameter selection.

were chosen to represent (1) the individual at the 40th percentile; (2) the individual at the 95th percentile; and (3) the individual at the 99th percentile (Fig. 5). The modeled concentration of TRI in expired air was plotted along with measurements of this value in human subjects (Stewart *et al.,* 1970; Fig. 3). All six simulated individuals representing the range of the distribution of the maximum value of the sum of [TRI] in blood and [TCOH] in its volume of distribution agreed well with the data. The greatest variability in expired air concentrations occurred during the postexposure periods (Fig. 3).

Because the dose metric is highly dependent on [TCOH], values for [TCOH] in blood were taken from two additional studies (Müller *et al.,* 1975; Vesterberg *et al.,* 1976). [TCOH] in the volume of distribution of simulated individuals was similar in time course and magnitude as the blood data obtained from the two human studies (Fig. 4).

Distribution of the Dose Metric in Men and Women

The maximum value of the sum of [TRI] and [TCOH] in blood was lognormally distributed in both men and women (Filliben, 1975; Fig. 5). The means of the two log-transformed distributions were not significantly different ($t_{[9998]} = 0.728$, $P > 0.3$). The highest level of the dose metric observed in males was 170.9 mg/L and in females it was 193.3 mg/L.

A threshold or target level of the dose metric could be either a statistic of the output distribution of dose metrics (Fig. 5) or an actual level of the maximum value of the sum of [TRI] and [TCOH] in blood known to represent a safe exposure. Sixty percent of the subjects in Stewart *et al.* (1970) reported feeling sleepy, and sleepiness may be of concern for an industrial worker. Therefore, if the simulated population accurately mirrored the experimental sample, 60% of the simulated population would also become "sleepy" at a dose of 200 ppm TRI for 7 h a day. Individuals at the 40th percentile of the dose metric or lower would not become "sleepy." Hence, the maximum value of the sum of [TRI] and [TCOH] in blood at the 40th percentile of the simulated population was chosen as *target* dose metric (Fig. 5; Table 6). To derive a guidance value based on the endpoint of drowsiness, the three moments of the distributions of most interest were the 40th percentile, the 95th percentile, and the 99th percentile (Fig. 5; Table 6).

Sedative doses of CH or TCOH administered to humans result in peak levels of TCOH in blood ranging 20 to 60 mg/L (Marshall and Owens, 1954). This observation corresponds well with the level of the target dose metric, approximately 16 mg/L in both males and females, above which drowsiness would occur.

The underlying assumption is that the simulated sample of men and women used in this Monte Carlo study is representative of the same population as the sample of six subjects used by Stewart *et al.* (1970) and also representative of the population of occupational receptors. The subjects in Stewart *et al.* (1970) were all young and healthy, and, similarly, no disease states were explicitly included in the human probabilistic parameters used

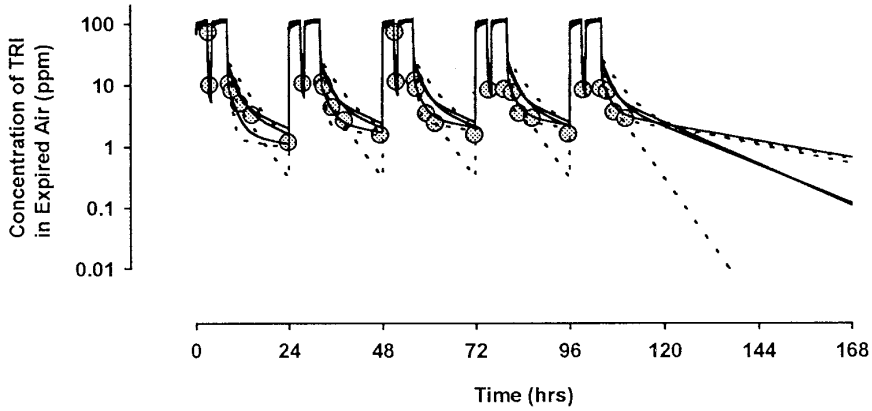

FIG. 3. Measured and modeled values of exhaled breath concentrations of TRI versus time in subjects receiving 200 ppm for 7 h a day. The gray filled circles are mean values from Stewart *et al.* (1970). Stewart *et al.* (1970) sampled only twice when the subjects were in the inhalation chamber. The three dotted lines are modeled values for males at the 40th, 95th, and 99th percentiles of the dose metric. The three solid lines are the corresponding modeled values for females. There is overlap of the lines during periods of exposure.

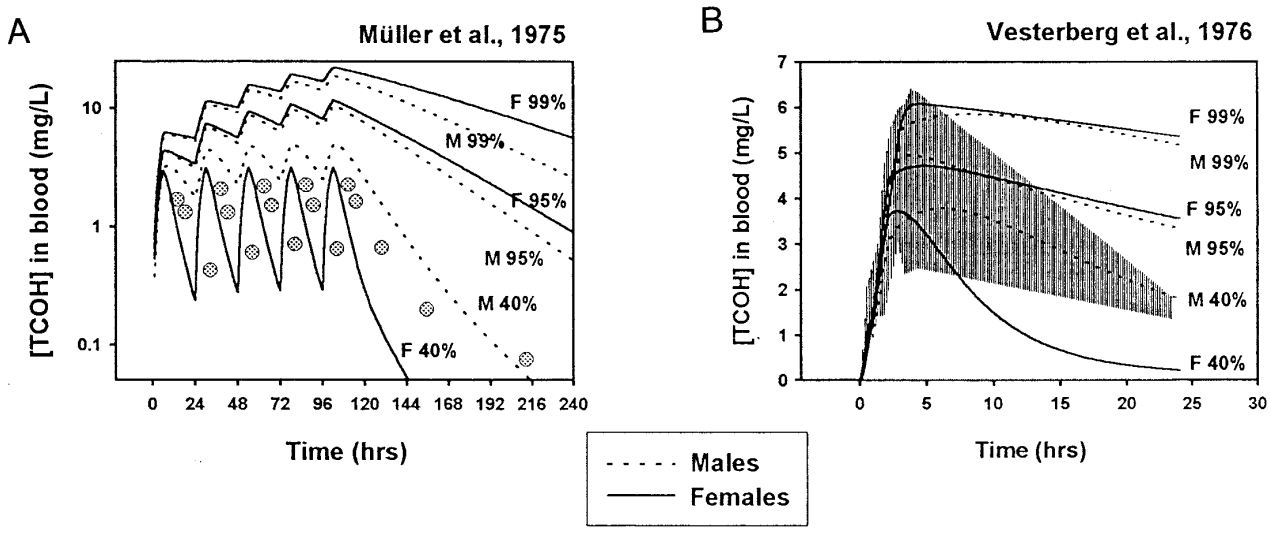

FIG. 4. Comparison of the time course of TCOH concentration in blood: modeled values and data from two independent studies. (A) The gray filled circles represent [TCOH] in blood in response to 50 ppm 6 h/day for 5 days (Müller *et al.*, 1975). The dotted and solid lines represent the responses of simulated males and females respectively. The traces are labelled to indicate the 40th, 95th, and 99th percentiles. (B) The gray shaded area represents the range of responses of volunteers to 180 min of exposure to 100 ppm TRI (Vesterberg *et al.*, 1976). The dotted and solid lines represent the responses of simulated males and females, respectively. In both A and B, the percentiles of the dose metric represented are labeled.

here. Both the simulated sample in this study and the sample from Stewart *et al.* (1970) could exhibit the "healthy-worker" effect in which working men and women tend to be more resilent to a variety of adverse effects than nonworkers (Wen *et al.*, 1983; Arrighi and Hertz-Piccioto, 1994). The relative health of the small experimental group of Stewart *et al.* (1970), the health of the general worker population and the fact that disease was explicitly excluded from the simulated population here suggest that the three may be comparable.

Sensitivity Analysis

Both rank correlation coefficients and multiple regression techniques were used to determine which parameters affected the dose metric. The two tech-

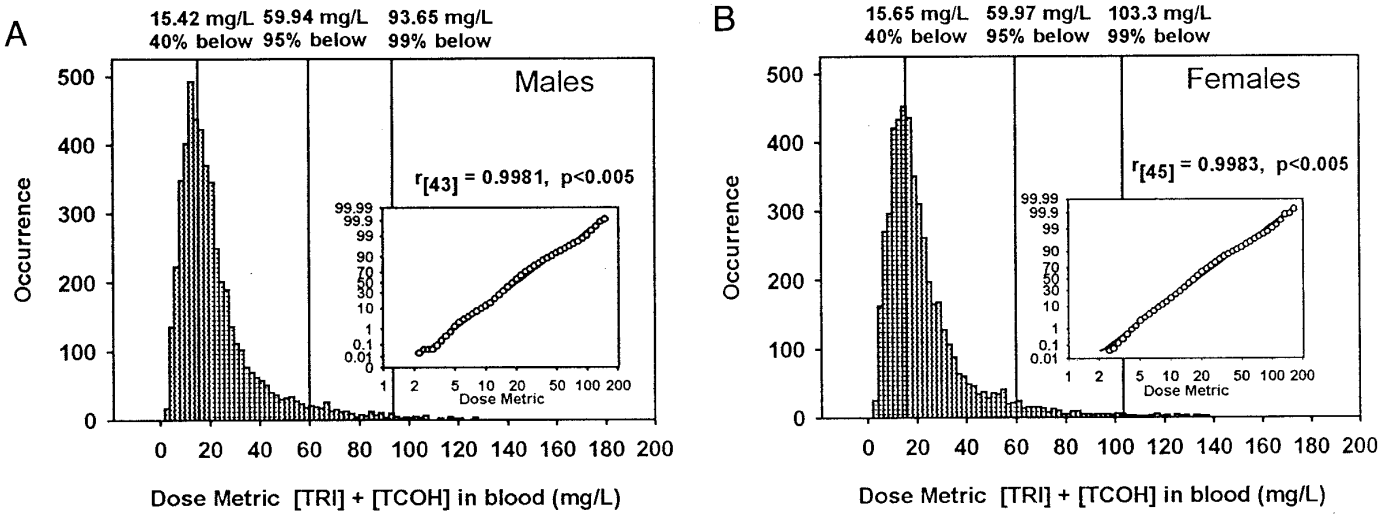

FIG. 5. Frequency distributions of the maximum value of the sum of [TRI] and [TCOH] in the blood of males and females. The 40th, 95th, and 99th percentiles are indicated. The insets are log-probability plots showing that both distributions are lognormal. The probability plot correlation coefficients (Filliben, 1975) are shown above the insets. (A) Distribution of the dose metric for 5000 simulated males. (B) Distribution of the dose metric for 5000 simulated females.

TABLE 6
Dose Metrics and Corresponding Air Concentrations

	Dose metric for the 40th percentile individual at 200 ppm TRI (mg/L)	Dose metric for the 95th percentile individual at 200 ppm TRI (mg/L)	Air concentration of TRI to reduce dose metric of 95th percentile individual to 40th percentile level (ppm)	Dose metric for the 99th percentile individual at 200 ppm TRI (mg/L)	Air concentration of TRI to reduce dose metric of 99th percentile individual to 40th percentile level (ppm)
Males	15.42	59.94	60	93.65	35
Females	15.65	59.97	50	103.28	30

Note. Values for the dose metric (maximum value of the sum of [TRI] and [TCOH] in blood) for males and females at the 40th, 95th, and 99th percentiles. Air concentrations of TRI needed to reduce the dose metric of individuals at the 95th and 99th percentiles to that of the individuals at the 40th percentile.

niques showed that the parameters, QCC, QPC, VMC, KMC, PO, VMOC, KMO, VMGC, and KUGC, were all significantly correlated with the dose metric (males, $F_{[9,4990]} = 852.78$, $P < 1E\text{-}06$; females, $F_{[9,4990]} = 789.22$, $P < 1E\text{-}06$). The most sensitive parameters were V_{max} and K_m for oxidation of TCOH to TCA (VMOC, KMO; Table 7).

Derivation of an Occupational Guidance Value

The basic procedure for deriving a safe exposure limit or guidance value was to identify a sensitive individual, i.e., one with a large value of the dose metric; such individuals are more sensitive in a toxicokinetic sense. This choice of which percentile to protect is, of course, a regulatory policy decision. Here, the individual at the 99th percentile was chosen as the sensitive individual, the one which will provide the basis of the guidance value derivation.

The model was performed iteratively using a similar 7 h/day occupational dosing regimen, and the air concentration of TRI was reduced until the dose metric experienced by the 99th percentile individual was just less than the dose metric experienced by the 40th percentile individual. A similar exercise was done to determine the reduction in air concentration for the 95th percentile individual. This exercise was performed for both males and females (Table 6).

The guidance values derived for females (50 ppm to protect 95% of workers; 30 ppm to protect 99% of workers) were chosen because they were lower than those for males and because of the increased acceptance of females in all work places. The method used to derive these values did not account for toxicodynamic uncertainty, the possibly different sensitivity of various individuals to the effects of the dose metric at the target tissue, but this is not believed to be a large factor (see Discussion).

For comparison, the ACGIH TLV-TWA is 50 ppm, a value that would protect 95% but not 99% of workers (ACGIH, 1991). The OSHA PEL was previously 50 ppm (OSHA, 1989a,b). In 1993, it was raised to 100 ppm, a value that would protect 78% of workers (OSHA, 1993).

Determination of the Length of Rest Needed after a 15-min Exposure at the Short-Term Exposure Limit (STEL)

ACGIH has indicated that a short-term exposure of 15 min to 200 ppm TRI is permissible. ACGIH considers this STEL to be 200 ppm. If two STELs of 200 ppm a day (morning and afternoon) are experienced by a worker who is also constantly exposed to 50 ppm, how much fresh air recovery time is needed following exposure to a STEL concentration? It was assumed that this twice a day exposure continued for a 5-day work week. The maximum value of the sum of [TRI] in blood and [TCOH] in its volume of distribution was deter-

TABLE 7
Sensitivity of the Dose Metric to Various Model Parameters

	Relative partial sum of squares (%)		Spearman rank correlation coefficient	
Parameter	Male	Female	Male	Female
VMOC	14.3	12.8	−0.573	−0.582
KMO	10.0	8.9	0.505	0.445
VMGC	5.6	5.6	−0.393	−0.402
QPC	3.3	3.1	0.338	0.333
PO	1.6	1.8	0.007	−0.141
VMC	1.6	1.3	0.133	0.096
QCC	0.55	0.6	0.295	0.268
KMC	0.36	0.24	0.057	0.036
KUGC	0.009	0.02	0.194	0.098

Note. Sensitivity of the dose metric to the nine most influential parameters of the model. The sensitivity was measured by (1) multiple regression and the relative partial sum of squares and (2) the Spearman rank correlation coefficient. The table is arranged by ranks of the influence of each parameter showing that the two methods are equivalent.

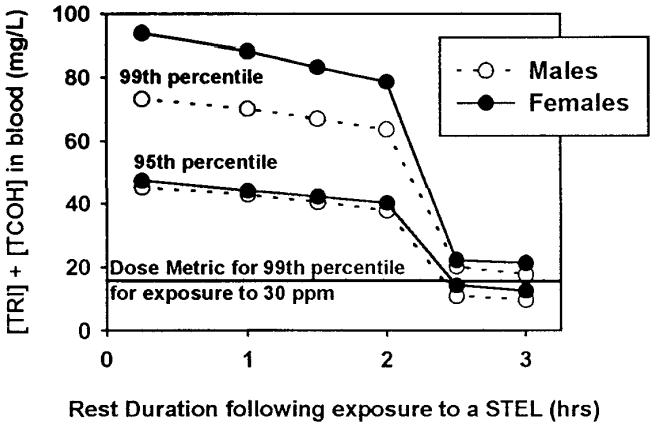

FIG. 6. Decline of the dose metric versus rest duration following twice a day exposure to 200 ppm TRI for 15 min. The two upper curves for males and females indicate the decline at the 99th percentile. The two lower curves indicate the decline at the 95th percentile. A 2.5-h rest in fresh air following exposure at the STEL is required for the dose metric to decline to levels that would not cause drowsiness in the 99th percentile individual.

mined for various rest durations following each STEL experience. A rest period of 2.5 h is needed to produce a reduction in the dose metric to levels that would not cause drowsiness (Fig. 6). This rest is long enough so that it includes the lunch break and abuts the end of the day.

The 95th percentile individuals (male and female) (but not the 99th percentile individuals) have dose metrics below the level of approximately 16 mg/L believed to cause drowsiness (Fig. 5). Therefore, it would be prudent for a worker to be exposed to no more than 2 STELs a day with a rest in fresh air of at least 2.5 h after each exposure to the STEL concentration.

DISCUSSION

Comparison with Other Guidance Values

Both the OSHA and ACGIH guidance values of 100 and 50 ppm, respectively, were derived empirically. The ACGIH TLV of 50 ppm protects against fatigue, headache, and irritability and was selected following a literature review to provide "a margin of safety" (ACGIH, 1991). OSHA selected a value of 50 ppm based on observations by NIOSH of industrial facilities at which exposures exceeded 50 ppm and symptoms of CNS disturbance were reported (OSHA, 1989a,b). Protection from carcinogenic effects was also considered. The reasons for increasing the value to 100 ppm were not made clear in the Air Contaminants Final Rule (OSHA, 1993). A recent study of cancer risk from TRI also suggests that both the OSHA and ACGIH guidance values are not expected to be protective (Bogen and Gold, 1997).

ATSDR derives MRLs using uncertainty factors. The acute inhalation MRL for TRI is 2 ppm and was derived from Stewart *et al.* (1970) using a neurobehavioral endpoint observed in 50% of the subjects. The combined uncertainty factor (UF) was 30: 3 for the use of a minimum LOAEL and 10 for human variability (ATSDR, 1995). The value was also corrected from 7 h per day to constant exposure. In the female at the 99th percentile of the dose metric, a steady-state level of the sum of [TRI] in blood and [TCOH] in its volume of distribution is reached in about 15 days. The safe exposure limit for this sensitive receptor undergoing constant exposure is 15 ppm.

Uncertainties in This Derivation

The sensitivity analysis reveals the parameters that influence the dose metric. The prime uncertainty in the guidance value derived here is the accuracy of the fitted parameter values for TCOH metabolism to TCA (VMOC and KMO) because they have the greatest influence on the dose metric (Table 7). Although there is not yet a direct measure of these enzyme parameters, the fact that the ranges of the fitted parameters derived from several data sets showed considerable overlap lends confidence to the values (Table 4).

Alcohol and/or aldehyde dehydrogenase may be the enzymes responsible for the conversion of TCOH to TCA and CH to TCOH. Both genetic and functional polymorphism exists for these enzymes (Agarwal and Goedde, 1992; Edman and Maret, 1992) and the V_{max} of alcohol dehydrogenase has been shown to vary at least 30-fold in African-Americans (Thomasson *et al.*, 1995). Considerably greater variability was observed in the fitted V_{max} values used in this study (VMOC, VMGC; Tables 3 and 4). Another factor is the levels of NADH and NAD^+ in the metabolizing tissue. The redox poise of the tissue may affect reaction rates and amounts of products formed (Barton *et al.*, 1996).

Deficiencies in glucuronidation such as Crigler–Najjar syndrome or Gilbert's syndrome would tend to increase levels of TCOH. It is unknown whether individuals with these diseases fall within the range of kinetic values for VMGC and KMG presented here. Possibly these individuals represent a sensitive subpopulation (Barton *et al.*, 1996).

In Lieu of Uncertainty Factors

The uncertainty factor for human variability is often used to account for sensitive subpopulations. It should be clear from this study that human variability within a given population (industrial workers in this study) is not the same thing as human variability based on a separate subpopulation that may be more or less susceptible to the effects of a chemical. The ratio of dose metrics for the individual at the 99th percentile and that for the individual at the 40th percentile can be

considered a data-derived toxicokinetic uncertainty factor for human variability within this population. This value is 6.1 for men and 6.6 for women.

Toxicological uncertainty may be apportioned into toxicokinetic and toxicodynamic factors (Renwick, 1991, 1993; Dourson *et al.*, 1996). The model used in this paper is a strictly toxicokinetic model, and the method reduces only toxicokinetic uncertainty. However, it has been suggested that a factor of 2.5 may account for toxicodynamic uncertainty (Renwick, 1993).

Application of this toxicodynamic UF to the guidance value of 30 ppm would result in a level of 12 ppm. The dose metric is dominated by TCOH and its effects are believed to result from a physicochemical mechanism, similar to ethyl alcohol in regard to drowsiness (Amdur *et al.*, 1993). The solvent behavior of both TRI and TCOH and indeed ethyl alcohol affects the fluidity of neuronal membranes and produces the effects of headache, fatigue, and drowsiness. There may be some toxicodynamic variability for these effects in humans, but because of the physicochemical mechanism, it is believed that the magnitude of this uncertainty is small, and application of an uncertainty factor to account for toxicodynamic differences is unnecessary.

Should the exact toxicodynamic mechanism of the sedative effect of TCOH become clear, the preferred method for amending the guidance values presented here would be to combine this toxicokinetic model with a toxicodynamic model with human parameters for which distributions are known or can be measured.

Estimates of the efficacy of the 10-fold UF for human variability indicate that it would protect between 86 and 96% of the human population (Dourson *et al.*, 1996). A UF of 10 applied to the exposure concentration of 200 ppm (Stewart *et al.*, 1970) would protect 100% of workers and would, in fact, be "overkill."

The uncritical application of UFs leads to overly conservative guidance values (e.g., ATSDR, 1995) and should be eschewed—the goal for a guidance value is protection of human health not excessive regulation. However, the needs of regulation are immediate, and *post hoc* validation of UFs has shown that the use of data-derived UFs is a great improvement until a more complete data-based analysis of each chemical can be performed (Dourson *et al.*, 1996). Guidance value derivation based on probabilistic estimates of UFs has been suggested (Baird *et al.*, 1996) and will likely also be effective in developing more realistic guidance values. UFs are in essence a tool of last resort. The exigencies of regulation are the basis of their embrace.

CONCLUSIONS

An occupational guidance value of 30 ppm for inhalation of trichloroethylene in the work place was derived. This level is lower than both the OSHA PEL and ACGIH TLV. The dose metric used to ascertain results of the PBPK modeling was the maximum value of the sum of [TRI] in blood and [TCOH] in its volume of distribution, and the endpoint selected was drowsiness. In addition to providing a new guidance value, another point of significance of the safe exposure level for TRI determined here is that no uncertainty factors were used in its derivation.

ACKNOWLEDGMENTS

I thank Dr. John Lipscomb for generously providing me the values for kinetic constants for oxidation of TRI by CYP2EI before their publication. I also thank Drs. Jeff Fisher and Hugh Barton for several helpful discussions. Drs. Richard Reitz, Michael Gargas, and Sean Hayes provided helpful comments early in this effort. I also thank Drs. Solomon Pollard, Cliff Opdyke, Michele Burgess, Linda Anderson-Carnahan, Marland Dulaney, and Rick Hertzberg for commenting on a draft of the manuscript.

REFERENCES

Agarwal, D. P., and Goedde, H. W. (1992). Pharmacogenetics of alcohol metabolism and alcoholism. *Pharmacogenetics* **2,** 48–62.

Agency for Toxic Substances and Disease Registry (ATSDR) (1995). *Toxicological Profile for Trichloroethylene,* draft for public comment (update). U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Allen, B. C., and Fisher, J. W. (1993). Pharmacokinetic modeling of trichloroethylene and trichloroacetic acid in humans. *Risk Anal.* **13**(1), 71–86.

Amdur, M. O., Doull, J., and Klaassen, C. D. (1993). *Casarett and Doull's Toxicology: The Basic Science of Poisons,* fourth ed. McGraw–Hill, New York.

American Conference of Governmental Industrial Hygienists (ACGIH) (1991). *Documentation of the Threshold Limit Values and Biological Exposure Indices,* 6th ed. ACGIH, Cincinnati, OH.

Arrighi, H. M., and Hertz-Piccioto, I. (1994). The evolving concept of the healthy worker survivor effect. *Epidemiology* **5,** 189–196.

Baird, J. S., Cohen, J. T., Graham, J. D., Shyakhter, A. I., and Evans, J. S. (1996). Noncancer risk assessment: Probabilistic characterization of population threshold doses. *J. Hum. Ecol. Risk Assess.* **2**(1), 79–102.

Barnes, D. G., and Dourson, M. L. (1988). Reference dose (RfD): Description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* **8,** 471–486.

Barton, H. A., Flemming, C. D., and Lipscomb, J. C. (1996). Evaluating human variability in chemical risk assessment: Hazard identification and dose–response assessment for noncancer oral toxicity of trichloroethylene. *Toxicology* **111,** 271–287.

Bogen, K. T., and Gold, L. S. (1997). Trichloroethylene cancer risk: Simplified calculation of PBPK-based MCLs for cytotoxic end points. *Regul. Toxicol. Pharmacol.* **25**(1), 26–42.

Butler, T. S. (1948). The metabolic fate of chloral hydrate. *J. Pharmacol. Exp. Ther.* **92,** 49.

Calabrese, E. J. (1985). Uncertainty factors and interindividual variation. *Regul. Toxicol. Pharmacol.* **5,** 190–196.

Clewell, H. J., Gentry, P. R., Gearhart, J. M., Allen, B. C., Covington, T. R., and Andersen, M. E. (1995). *Applying Mechanistic Information, Pharmacokinetic Modeling and Margin of Exposure Evaluations in a Novel Risk Assessment for Trichlorethylene and Its Active Carcinogenic Metabolites: Chloral Hydrate, Trichloroacetic Acid, Dichloroacetic Acid, and Dichlorovinylcysteine.* K.S. Crump Division, ICF Kaiser Int'l, prepared for OSHA Directorate of Health

Standards Program and EPA Office of Health and Environmental Assessment.

Cronin, W. J., IV, Oswald, E. J., Shelley, M. L., Fisher, J. W., and Flemming, C. D. (1995). A trichloroethylene risk assessment using a Monte Carlo analysis of parameter uncertainty in conjunction with physiologically-based pharmacokinetic modeling. *Risk Anal.* **13**(5), 555–565.

Dekant, W., Metzler, M., and Henschler, D. (1984). Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. *Biochem. Pharmacol.* **33,** 2021–2027.

Dekant, W., Schultz, A., Metzler, M., and Henschler, D. (1986). Absorption, elimination, and metabolism of trichloroethylene: A quantitative comparison between rats and mice. *Xenobiotica* **16,** 143–152.

Dourson, M. L., and Stara, J. F. (1983). Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.* **3,** 224–238.

Dourson, M. L., Felter, S. P., and Robinson, D. (1996). Evolution of science-based uncertainty factors in noncancer risk assessment. *Regul. Toxicol. Pharmacol.* **24,** 108–120.

Edman, K., and Maret, W. (1992). Alcohol dehydrogenase genes: Restriction fragment length polymorphisms for ADH-4 (pi-ADH) and ADH-5 (chi-ADH) and construction of haplotypes among different ADH classes. *Hum. Genet.* **90,** 395–401.

Filliben, J. J. (1975). The probability plot correlation coefficient test for normality. *Technometrics* **17**(1), 111–117.

Fiserova-Bergerova, V., Vlach, J., and Cassady, J. C. (1980). Predictable "individual differences" in uptake and excretion of gases and lipid soluble vapours simulation study. *Br. J. Ind. Med.* **27,** 42–49.

Fisher, J. W., and Allen, B. C. (1993). Evaluating the risk of liver cancer in humans exposed to trichloroethylene using physiological models. *Risk Anal.* **13**(1), 87–95.

Fisher, J. W., Gargas, M. L., Allen, B. C., and Andersen, M. L. (1991). Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse. *Toxicol. Appl. Pharmacol.* **109,** 183–195.

Fisher, J. W., Pleil, J., MacMahon, K., and Abbas, R. (1997). A physiologically based pharmacokinetic model for inhalation of trichloroethylene in human volunteers. *The Toxicologist* **36**(1), 32.

Gargas, M. L. (1996). *Variability of Partition Coefficients of Trichloroethylene,* private communication, Dr. Michael L. Gargas, McLaren-Hart/ChemRisk, Cleveland, OH.

Gargas, M. L., Burgess, R. J., Voisard, D. E., Cason, G. H., and Andersen, M. E. (1989). Partition coefficients of low molecular weight volatile chemicals in various liquids and tissues. *Toxicol. Appl. Pharmacol.* **98,** 87–99.

Green, J. F. (1987). *Fundamental Cardiovascular and Pulmonary Physiology,* second ed. Lea & Febiger, Philadelphia.

Hattis, D., and Silver, K. (1994). Human interindividual variability—A major source of uncertainty in assessing risks for noncancer health risks. *Risk Anal.* **14**(4), 421–431.

International Commission of Radiological Protection (ICRP) (1975). *Report of the Task Group on Reference Man.* Pergamon, New York.

International Life Sciences Institute (ILSI) (1994). *Physiological Parameter Values for PBPK Models,* a report prepared under a cooperative agreement with the USEPA Office of Health and Environmental Assessment [unpublished]

Kyrkland, T., Alling, C., Haglid, K., and Kjellstand, P. (1983). Chronic exposure to trichloroethylene: Lipid and acyl group composition in gerbil cerebral cortex and hippocampus. *Neurotoxicology* **4**(4), 35–42.

Lipscomb, J. C., Mahle, D. A., Brashear, W. T., and Garrett, C. M. (1996). A species comparison of chloral hydrate metabolism in blood and liver. *Biochem. Biophys. Res. Commun.* **227,** 340–350.

Lipscomb, J. C., Garrett, C. M., and Snawder, J. E. (1997). Cytochrome P450-dependent metabolism of trichloroethylene: Interindividual differences in humans. *Toxicol. Appl. Pharmacol.* **142**(2), 311–318.

Lipton J., Shaw, W. D., Holmes, J., and Patterson, A. (1995). Short communication: Selecting input distributions for use in Monte Carlo simulations. *Regul. Toxicol. Pharmacol.* **21,** 192–198.

Marshall, E. K., and Owens, A. H. (1954). Absorption, excretion and metabolic fate of chloral hydrate and trichloroethanol. *Bull. Johns Hopkins Hosp.* **95,** 1–18.

Müller, G., Spassowski, M., and Henschler, D. (1974). Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. *Arch. Toxicol.* **32,** 283–295.

Müller, G., Spassowski, M., and Henschler, D. (1975). Metabolism of trichloroethylene in man. III. Interaction of trichloroethylene and alcohol. *Arch. Toxicol.* **33,** 173–189.

OSHA (1989a). Trichloroethylene: Occupational safety and health administration. *Fed. Reg.* **54,** S101–S103.

OSHA (1989b). Air contaminants final rule: Occupational safety and health administration. *Fed. Reg.* **54,** 2332–2960.

OSHA (1993). Air contaminants final rule: Occupational safety and health administration. *Fed. Reg.* **58,** 35338–35351.

Pierce, C. H., Dills, R. L., Morgan, M. S., Nothstein, G. L., Shen, D. D., and Kalman, D. A. (1996). Interindividual differences in $^{2}H_{8}$-toluene toxicokinetics assessed by a semiempirical physiologically based model. *Toxicol. Appl. Pharmacol.* **139,** 49–61.

Press, H., Teukolsky, S. A., Flannery, B. P., and Vetterling, W. T. (1986). *Numerical Recipes: The Art of Scientific Computing.* Cambridge Univ. Press, Cambridge.

Reitz, R. H., Gargas, M. L., Mendrala, A. L., and Schumann, A. M. (1996). *In vivo* and *in vitro* studies of perchlorethylene metabolism for physiologically based pharmacokinetic modeling in rats, mice and humans. *Toxicol. Appl. Pharmacol.* **136,** 289–306.

Renwick, A. G. (1991). Safety factors and establishment of acceptable daily intake. *Food Add. Contam.* **8**(2), 135–150.

Renwick, A. G. (1993). Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Add. Contam.* **10**(3), 275–305.

Rose, K. A., Smith, E. P., Gardner, R. H., Brenkert, A. L., and Bartell, S. M. (1991). Parameter sensitivities, Monte Carlo filtering, and model forecasting under uncertainty. *J. Forecasting* **10,** 117–133.

Rutishauer, I. H. E., Pasco, J. A., and Wheeler, C. E. (1995). The influence of body build on estimates of body composition from anthropometric measurements in premenopausal women. *Eur. J. Clin. Nutr.* **49,** 248–255.

Salvini, M., Binaschi, S., and Riva, M. (1971). Evaluation for the psychophysiological functions in humans exposed to trichloroethylene. *Br. J. Ind. Med.* **28,** 293–295.

Sato, A., Nakajima, T., Fujiwara, Y., and Murayama, N. (1977). A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure. *Br. J. Ind. Med.* **34,** 56–63.

Sellers, E. M., Lang-Sellers, M., and Koch-Weser, J. (1978). Comparative metabolism of chloral hydrate and triclofos. *J. Clin. Pharmacol.* **18,** 457–461.

Simulation Resources, Inc. (1996). *Manual for SCoP Simulation Control Program: A General Purpose Simulation Package,* Version 3.51. Berrien Springs, MI.

Stewart, R. D., Dodd, H. C., Gay, H. H., and Erley, D. S. (1970). Experimental human exposure to trichloroethylene. *Arch. Environ. Health* **20,** 64–71.

Stewart, R. D., Hake, C. L., Le Brun, A. J., Peterson, J. E., Forster, H., Hosko, M. J., Newton, P. E., Soo, R. J., Dodd, H. D., Graff, S., Donohoo, K. K., and Mellender, J. (1974). *Biological Standards for*

the Industrial Worker by Breath Analysis: Trichloroethylene, HEW Publication No. 74–126. National Institute for Occupational Safety and Health, Cincinnati, OH.

Stoudt, H. W., Damon, A., and Ramsey, J. C. (1960). Heights and weight of white Americans. *Hum. Biol.* **32,** 331–341.

Thomas, R. S., Bigelow, P. L., Keefe, T. J., and Yang, R. S. H. (1996a). Variability in biological exposure indices using physiologically based pharmacokinetic modeling and Monte Carlo simulation. *Am. Ind. Hyg. Assoc. J.* **57,** 23–32.

Thomas, R. S., Lytle, W. E., Keefe, T. J., Constan, A. A., and Yang, R. S. H. (1996b). Incorporating Monte Carlo simulation into physiologically based pharmacokinetic models using advanced continuous simulation language (ACSL): A computational method. *Fundam. Appl. Toxicol.* **31,** 19–28.

Thomasson, H. R., Beard, J. D., and Li, T. K. (1995). ADH2 gene polymorphisms are determinants of alcohol pharmacokinetics. *Alcohol Clin. Exp. Res.* **19**(6), 1494–1496.

USEPA (1994). *Guidance Manual for the Integrated Exposure Uptake Biokinetic Model for Lean in Children*, OSWER Publication 9285.7-15-1, **EPA/540/R-93/081.**

USEPA (1997). *Integrated Risk Information System*. [Computer database on human toxicity.]

Vesterberg, O., Gorczak, J., and Krasts, M. (1976). Exposure to trichloroethylene. II. Metabolites in blood and urine. *Scand. J. Work Environ. Health* **4,** 212–219.

Wen, C. P., Tsai, S. P., and Gibson, R. L. (1983). Anatomy of the healthy worker effect: A critical review. *J. Occup. Med.* **25,** 283–289.

Williams, L. R., and Leggett, R. W. (1989). Reference values for resting blood flow to organs of man. *Clin. Phys. Meas.* **10,** 187–217.