

**Supplemental Material**

**for**

**Issues in the Pharmacokinetics of Trichloroethylene and Its Metabolites**

Weihsueh A. Chiu, Miles S. Okino, John C. Lipscomb, and Marina V. Evans

## Supplemental Material

This manuscript has focused on research efforts published since the 2000 state-of-the-science monograph, including past research relevant to those efforts. These supplemental materials provide a comprehensive description of pharmacokinetic studies on TCE and its metabolites and PBPK models for TCE.

Supplemental Table S-1 “Summary of *in vivo* studies of trichloroethylene (TCE) pharmacokinetics” includes descriptions of the pharmacokinetic studies on TCE and its metabolites in mice, rats, and humans. The dosing scenarios are listed along with the measurements taken in each study. The table also indicates the PBPK models that used multiple data sets for calibration and evaluation. The PBPK models that used only a single data set collected by the authors are not included.

Supplemental Table S-2 “Summary of PBPK models of trichloroethylene (TCE) and metabolites” provides summaries of published PBPK models. The species, exposure routes, compartments, and metabolites simulated in the models are listed for comparison. Many of the PBPK models have been used for subsequent analyses, although those efforts are not detailed in this table.

**Table S-1. Summary of *in vivo* studies of trichloroethylene (TCE) pharmacokinetics**

Reference	Species (Strain, if appl.)	Sex (M, F, M+F)	Exposures		Reported Measurements			Physiologically based pharmacokinetic models analyzing multiple datasets													
			TCE	Other (if appl.)	TCE	TCA	TCOH/TCOQ(a)	Other	Bois 2000a	Bois 2000b	Clewell et al. 2000	Clewell et al. 2004	Fisher 2000	Greenberg et al. 1999	Hack et al. 2004	Keys et al. 2003	Lapare et al. 1995	Slenner et al. 1988	Thrail and Poet 2000		
<i>Human studies</i>																					
Bartolisek 1962	Human	M+F	Inhalation		exhaled air	plasma, red cells, urine, sweat, saliva	urine, sweat, saliva	TCOH+TCA in feces													
Bernaer et al. 1996	Human	M	Inhalation		--	urine	--	TCA, TCOH in urine, NADCVG in urine													
Bloemen et al. 2001	Human	M	Inhalation		uptake	urine	urine	NADCVG in urine													
Erle et al. 1972	Human	M	Inhalation		--	urine	blood, urine														
Fernandez et al. 1977	Human	M	Inhalation		alveolar air	urine	urine														
Fisher et al. 1998	Human	M+F	Inhalation		exhaled air, blood	blood, urine	blood (H), urine (G)	CH in blood, DCA, plasma													X(b)
Kimmerle and Eben 1973b	Human	M+F	Inhalation		exhaled air, blood	urine	blood, urine	CH in blood													
Lapare et al. 1995	Human	M+F	Inhalation		alveolar air, blood	urine	urine														
Lash et al. 1999	Human	M+F	Inhalation		--	urine	urine														
Monster et al. 1976	Human	M	Inhalation		exhaled air, blood	blood, urine	blood, urine	DCVVG in blood													
Monster et al. 1979	Human	M	Inhalation		exhaled air, blood	blood, urine	blood, urine														
Müller et al. 1972	Human	ns	Inhalation		--	plasma, urine	blood, urine														
Müller et al. 1974	Human	M	Inhalation		alveolar air, blood	plasma, urine	blood, urine														
Müller et al. 1975	Human	M	Inhalation		alveolar air, blood	plasma, urine	blood, urine	ethanol, acetaldehyde in blood													
Paykoc et al. 1945	Human	ns	--		--	blood, plasma, urine	--														
Poet et al. 2000	Human	M+F	Dermal		exhaled air	urine	urine														
Sato et al. 1977	Human	M	Inhalation		alveolar air, blood	urine	urine														
Sato and Nakajima 1978	Human	M	Dermal		alveolar air, blood	urine	urine														
Soucek and Vlachova 1960	Human	M+F	Inhalation		retention	urine	urine	MCA in urine													
Stewart et al. 1970	Human	ns	Inhalation		alveolar air	urine	urine														
Vesterberg and Astrand 1976(d)	Human	M	Inhalation		alveolar air, arterial and venous blood	blood, urine	blood, urine														
<i>Mouse studies</i>																					
Abbas et al. 1996	Mouse (B6C3F1)	M	--		CH iv	blood	blood (H,G)	CH in blood, AUC, CH in liver, DCA in blood													
Abbas and Fisher 1997	Mouse (B6C3F1)	M	Oral (corn oil)			blood, liver, kidney, urine	blood (H,G) liver (H,G), lung (H), kidney (H,G), urine (G)	OH in blood, liver, lung, kidney; DCA in blood, liver, kidney													
Barton et al. 1999	Mouse (B6C3F1)	M	--		DCA iv and oral (aqueous)	--	--	DCA in blood													
Birner et al. 1993	Mouse (NMR1)	M+F	Garage (ns)		--	urine	--	NADCVG in urine													
Fisher and Allen 1993	Mouse (B6C3F1)	M+F	Garage (corn oil)		blood	plasma	plasma														
Fisher et al. 1991	Mouse (B6C3F1)	M+F	Inhalation		blood, closed chamber	plasma	plasma														
Fisher et al. 1991	Mouse (B6C3F1)	M+F	Garage (corn oil)		exhaled air	urine	urine	%dose as urine, feces, CO2													
Green and Prout 1985	Mouse (B6C3F1)	M	Garage (corn oil)		exhaled air, blood, liver, kidney, lung, fat	blood, liver, kidney, plasma, urine	blood (H,G) liver (H,G), lung (H), kidney (H,G) plasma, urine	CH in blood, liver, lung, kidney; DCA in blood, liver, kidney													
Greenberg et al. 1999	Mouse (B6C3F1)	M	Inhalation		--	urine	urine														
Larson and Bull 1992a	Mouse (B6C3F1)	M	--		DCA, TCA oral (aqueous)	blood, liver, kidney, lung, fat	blood (H,G) liver (H,G), lung (H), kidney (H,G) plasma, urine	%dose as urine, feces, CO2; DCA in plasma, urine; TDA, MCA in urine													
Larson and Bull 1992b	Mouse (B6C3F1)	M	Oral (aqueous)		blood	blood	blood (H)	DCA in blood													
Merdink et al. 1998	Mouse (B6C3F1)	M	Oral (aqueous)		iv	blood	blood (H)	CH in blood													
Prout et al. 1985	Mouse (B6C3F1, Swiss)	M	Garage (corn oil)		exhaled air, blood	blood	blood (-)	CHL in blood, %dose as urine, feces, CO2 carcass													
Templin et al. 1993	Mouse (B6C3F1)	M	Oral (aqueous)		blood	blood	blood (H, G)	DCA in blood													

**Table S-1. Summary of *in vivo* studies of trichloroethylene (TCE) pharmacokinetics (cont.)**

Reference	Species (Strain, if appl.)	Sex (M, F, M+F)	Exposures		Reported Measurements				Physiologically based pharmacokinetic models analyzing multiple datasets													
			TCE	Other (if appl.)	TCE	TCA	TCOH/TCOG[a]	Other	Allen and Fisher 1993	Bois 2000a	Bois 2000b	Clewell et al. 2000	Clewell et al. 2004	Fisher 2000	Greenberg et al. 1999	Hack et al. 2004	Keys et al. 2003	Lapare et al. 1995	Stenner et al. 1998	Thrall and Poet 2000		
<i>Rat studies</i>																						
Andersen et al.1987	Rat (Fisher)	M	Inhalation		closed chamber	--	--	--						X							X	
Barton et al.1995	Rat (SD)	M	Inhalation		closed chamber	--	--	--														
Bernauer et al.1996	Rat (Wistar)	M	Inhalation		--	--	--	--	TCA+TCOH in urine, NADCVC in urine				X	X							X	
Birner et al.1993	Rat (Wistar, Fisher 344)	M+F	Gavage (ns)		--	urine	--	--	NADCVC in urine													
Dallas et al.1991	Rat (SD)	M	Inhalation		exhaled air, blood	--	--	--														
D'Souza et al.1985	Rat (SD)	M	iv, oral (aqueous)		blood	--	--	--														
Fisher et al.1991	Rat (Fisher 344)	M+F	Inhalation		blood	plasma	--	--					X	X	X						X	
Green and Prout 1985	Rat (Osborne-Mendel)	M	Gavage (corn oil)	TCA gavage (aqueous)	exhaled air	urine	urine	urine	%dose as urine, feces, CO2													
Hissink et al.2002	Rat (Wistar)	M	Gavage (corn oil), iv		blood	--	--	--	%dose as urine, feces, expired air; radioactivity in organs													
Jakobson et al.1986	Rat (SD)	F	Inhalation	Pretreatment (oral) with ethanol, other chemicals	blood	--	--	--														
Kaneko et al.1994	Rat (Wistar)	M	Inhalation	Pretreatment (oral) with ethanol	blood	urine	urine	urine														
Keys et al.2003	Rat (SD)	M	Inhalation, oral (aqueous), ia		blood, liver, fat, kidney, lung, muscle, GI, brain, heart, exhaled air, blood, fat, brain, liver, kidney, spleen, heart	--	--	--													X	
Kimmerle and Eben 1973a	Rat (Wistar)	M	Inhalation		urine	blood, urine	blood, urine	CH in blood														
Larson and Bull 1992a	Rat (Fisher 344)	M	--	DCA, TCA oral (aqueous)	--	plasma, urine	plasma, urine	%dose as urine, feces, CO2; DCA in plasma, urine; TDAA, MCA in urine					X	X	X							X
Larson and Bull 1992b	Rat (SD)	M	Oral (aqueous)		blood	blood	blood (H)	DCA in blood					X									X
Lee et al.1996	Rat (SD)	M	Arterial, venous, portal, stomach injections		blood	--	--	--														
Lee et al.2000	Rat (SD)	M	Stomach injection	pretreatment (ia) with p-nitrophenol	blood	--	--	--														
Merdink et al.1999	Rat (Fisher 344)	M	--	CH, TCOH iv	--	blood, bile	blood (H, G), bile (G)	CH in blood, bile														X
Poet et al.2000	Rat (Fisher 344)	M	Dermal		chamber	--	--	--														
Prout et al.1985	Rat (Osborne-Mendel, Wistar)	M	Gavage (corn oil)		exhaled air, blood	blood	blood (-)	CHL in blood, %dose as urine, feces, CO2, carcass					X	X	X							X
Saghir et al.2002	Rat (Fisher 344)	M	--	DCA iv, oral (aqueous)	--	--	--	DCA in plasma														
Simmons et al.2002	Rat (Long-Evans)	M	Inhalation		closed chamber, blood, liver, brain, fat	--	--	--														
Stenner et al.1997	Rat (Fisher 344)	M	intraduodenal	TCOH, TCA iv	--	blood, bile	blood, bile	--														X
Templin et al.1995	Rat (Fisher 344)	M	Oral (aqueous)		blood	blood	blood, bile (H,G)	--						X	X							X
Thrall et al.2000	Rat (Fisher 344)	M	iv	with toluene	exhaled breath, closed chamber	--	--	--														X

**Notes:** [a] Combined free+bound unless otherwise specified [(H) = free only, (G) = bound only, (H,G) = both, separately]  
 [b] Subset of individuals used  
 [c] Implicit through use of Bois-Clewell posteriors as priors  
 [d] Summary of data reported in Astrand and Ovrum (1976) and Vesterberg et al. (1976)  
 ns= not specified

**Abbreviations:** AUC = area under the concentration curve; CH = chloral hydrate; CHL = chloral; CO2 = carbon dioxide; DCA = dichloroacetic acid; DCVC = *S*-dichlorovinyl-L-cysteine; DCVG = *S*-dichlorovinyl glutathione; iv = intravenous; MCA = monochloroacetic acid; NADCVC = *N*-acetyl DCVC; SD = Sprague-Dawley; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol; TCOG = TCOH glucuronide; TDAA = thiodiacetic acid

**Table S-2: Summary of physiologically based pharmacokinetic models of trichloroethylene (TCE) and metabolites**

Reference	Species (Strain, if appl.)	Sex	Exposure scenarios		TCE compartments[a]								TCA compartments[b]					Other metabolites/compartments					
			TCE	Other	fat	GI	kidney	liver	lung	rapidly perfused	slowly perfused	other	body	kidney	liver	lung	Vdist	other	TCOH	TCOG	DCA	CHL/CH	DCVC
Abbas and Fisher 1997	Mice B6C3F1	Male	oral		x	2	x	x	x	x	x		x	x	x	x			same as TCA	same as TCA	same as TCA	same as TCA	
Allen and Fisher 1993	Human		inhalation		x			x	x	x	x											x	
Andersen et al. 1987	Rats F344	Male	inhalation	inhaled TCE with DCE	x			x	x	x	x												
Barton et al. 1999	Mice B6C3F1	Male		chronic oral DCA, acute iv DCA																		body, GI, liver	
Clewell et al. 2000	Mice, Rat, Human		inhalation and oral		x	2		x	x	x	x											x	Vdist, lung, Vdist
Clewell et al. 2004 [c]	Mice, Rat, Human		inhalation, iv, oral		x	2		x	x	x	x			x								x	Vdist, lung, Vdist
Dallas et al. 1991	Rat SD	Male	inhalation		x			x	x	x	x												
Fernandez et al. 1977	Human	Male	inhalation		x			x	x	x	x											x	Vdist, Vdist
Fisher et al. 1989	Rat F344	Female, pregnant	inhalation and oral	iv TCA	x	x		x	x	x	x			x									placenta, fetus
Fisher et al. 1990	Rat F344; adult and lactating	Female, lactating	inhalation and oral		x	x		x	x	x	x			x									mammary tissue, milk
Fisher et al. 1991	Mice B6C3F1; Rats F344	Female and Male	inhalation		x			x	x	x	x											x	
Fisher et al. 1998	Human	Female and Male	inhalation		x			x	x	x	x			x	x	x	x						same as TCA, Vdist
Greenberg et al. 1999	Mice B6C3F1	Male	inhalation		x			x	x	x	x			x	x	x	x						same as TCA, same as TCA, same as TCA, same as TCA
Keys et al. 2003	Mice B6C3F1; Rats SD	Male	inhalation, ia injection, oral		2	x	x	2	x	x	x												brain, heart, spleen
Keys et al. 2004	Mice B6C3F1; Rats F344	Male		chronic oral DCA, acute iv DCA																			kidney, liver, rapidly perf,
Koizumi 1989	Rats OM; Human	Male	inhalation and oral		x			x	x	x	x												
Lapare et al. 1995	Humans		inhalation		x	x		x	x	x	x											x	Vdist
Poet et al. 2000	Rat F344, Humans	Male rats; Female	dermal		x			x	x	x	x												skin
Sato et al. 1991	Human	Female and Male	inhalation		x	x		x	x	x	x											x	muscle, Vdist
Simmons et al. 2002	Rats long-evans	Male	inhalation		x			x	x	x	x												brain
Stenner et al. 1998	Rats F344	Male	oral	iv CH, TCA, TCOH	x	x		x	x	x	x											x	fat, GI, rapid perf, slow perf, bile, fat, GI, rapid perf, slow perf, GI, rapid perf, slow perf, bile
Thrall and Poet 2000	Rats F344	Male	iv, ip injection	iv TCE with toluene	x			x	x	x	x												

**Notes:** [a] "2" indicates a 2-compartment organ  
 [b] Vdist=volume of distribution  
 [c] Development of a physiologically-based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Report prepared for U.S. Air Force. Available from: <http://www.tera.org/vera/TCE/TCE%20PBPK%20harmonization%20document>.

**Abbreviations:** CH = chloral hydrate; CHL = chloral; DCA = dichloroacetic acid; DCVC = S-dichlorovinyl-L-cysteine; ia = intraarterial; ip = intraperitoneal; iv = intravenous; GI = gastrointestinal; OM = Osborne-Mendel; SD = Sprague-Dawley; TCA = trichloroacetic acid; TCE = trichloroethylene; TCOH = trichloroethanol; TCOG = TCOH glucuronide

## References for Supplemental Materials

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