CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Information on the toxicokinetics of 1,1,1-trichloroethane is available from a small number of human studies and several animal studies; a brief summary of findings is provided below.

- 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. Rapid and passive diffusion of 1,1,1-trichloroethane across cell membranes is facilitated by the chemical's lipophilicity and low molecular weight.

- Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues.

- 1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine, and other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure.

- The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

3.1.1 Absorption

Data from experiments in which humans were exposed for short periods to 1,1,1-trichloroethane vapors indicate that the compound is rapidly and extensively absorbed by the respiratory system. 1,1,1-Trichloroethane was detected in the arterial blood of men within ≈10 seconds after exposure to 250 or 350 ppm (Astrand et al. 1973). When subjects held single breaths of air containing radiolabeled 1,1,1-trichloroethane for 15–40 seconds, alveolar concentrations decreased to between 10 and 20% of the initial concentrations, indicating extensive absorption upon initial exposure (Morgan et al. 1972a, 1972b). Human studies on 1,1,1-trichloroethane use exhaled breath, blood, or urine as surrogates for estimating the exposure dose of 1,1,1-trichlorethane. Droz et al. (1988) exposed volunteers to 1,1,1-trichloroethane that was detected in breath for up to15 hours postexposure after inhalation of 200 ppm 1,1,1-trichloroethane. Nagatoshi et al. (1994) concluded that worker exposure was extremely small in factories that

exercised proper control over exposure to 1,1,1-trichloroethane and other solvents. Nolan et al. (1984) used both blood and expired air concentrations of 1,1,1-trichloroethane to validate absorption of the chemical via inhalation exposure after a 6-hour exposure. Correlations between absorption via inhalation exposure to 1,1,1-trichloroethane and blood concentrations have been observed in numerous studies (Gill et al. 1991; Hajimiragha et al. 1986; Monster and Houtkooper 1979; Tay et al. 1995).

The extent of absorption of inhaled 1,1,1-trichloroethane decreases with continued exposure to the compound, as concentrations in alveolar air, blood, and tissues attain near equilibrium or steady state. Average lung retentions of 25–30% were measured in humans exposed to 35–350 ppm for 4–6 hours (i.e., the concentration of 1,1,1-trichloroethane in expired air after 4–6 hours of exposure equaled 70–75% of the inspired concentration) (Monster et al. 1979; Nolan et al. 1984). The concentration in blood increased rapidly in the first 1.5 hours, which was 90% of the peak of the systematic uptake (Nolan et al. 1984). Physical exercise during 0.5–4-hour exposures increased systemic absorption of 1,1,1-trichloroethane, due to increased alveolar ventilation and cardiac output (Astrand et al. 1973; Monster et al. 1979). A physiologically-based pharmacokinetic (PBPK) model developed by Laparé et al. (1995) suggested that a 10-minute workload increases alveolar uptake of 1,1,1-trichloroethane by 12%. While steady-state levels in blood are approached within the first hours after exposure begins (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984), Nolan et al. (1984) predicted, using a physiologically-based kinetic model, that 12 consecutive 6-hour daily exposures (presumably to concentrations of 350 ppm) would be required for 1,1,1-trichloroethane in body tissues to reach 95% of steady state. A more recently developed physiological kinetic model predicted that steady-state venous blood concentrations of 1,1,1-trichloroethane would be achieved within 14 days after exposure levels in the range of 10–5,000 ppm based on the Reitz et al. (1988) model (EPA 2006a; Lu et al. 2008). These studies also predicted that 94% of steady-state blood concentration would be reached within 4 days and 98% of steady-state would be reached within 7 days. Absorption is expected to be relatively low after steady state is reached because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading, which in turn is affected by respective blood:air and tissue:blood partition coefficients, tissue volumes and blood flows, and low metabolism (Johns et al. 2006; Reitz et al. 1988). Blood:air partition coefficients for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively (Reitz et al. 1988), meaning that small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Mice also have the highest respiratory and circulatory rates, two additional factors that significantly influence systemic absorption of 1,1,1-trichloroethane. 1,1,1-Trichloroethane is poorly metabolized in humans and animals (see Section 3.1.3).

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate (Schumann et al. 1982; Dallas et al. 1989; Gargas et al. 1986; Warren et al. 1998; You and Dallas 2000). In rats exposed to 50 or 500 ppm, the percentage uptake decreased from ~80% at the onset of exposure to ~50% after 2 hours post-exposure. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In rats exposed to 1,000–5,000 ppm, 1,1,1-trichloroethane was rapidly absorbed by the lungs within 10 minutes of inhalation exposure and achieved equilibrium in the blood and brain within 40 minutes during a 100-minute inhalation exposure to 1,000 or 2,000 ppm (Warren et al. 1998). In mice and rats exposed to 3,500 and 5,000 ppm, 1,1,1-trichloroethane concentrations in blood increased rapidly during the first 10 minutes, and the concentrations measured after an hour were >90% of the concentrations measured after 2 hours (You and Dallas 1998). Concentrations at steady state were achieved also within 2 hours (You and Dallas 1998). The blood 1,1,1-trichloroethane concentration in mice increased more rapidly than that in rats for the first 10 minutes and was significantly higher in mice at 1- and 2-hours post-exposure to either concentration administered (You and Dallas 1998). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983a, 1983b).

Data regarding the rate or extent of absorption of ingested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 7–15 minutes of gavage administration of a 6–48-mg/kg dose in water (Mortuza et al. 2018; Reitz et al. 1988). In experiments in which rats were given 8-hour free access to drinking water containing [2–14C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI 1987). After administration of 22.5–30 mmol/kg oral dose of 1,1,1-trichloroethane in rats and mice, 88–98% of doses were recovered through expired air and urine in 48 hours (Mitoma et al. 1985).

Mortuza et al. (2018) estimated a high portion of systemic uptake after doses of 6 and 48 mg/kg of aqueous emulsions of 1,1,1-trichloroethane by gavage and gastric infusion, respectively, over 2 hours in rats. Peak blood levels were obtained within 8 minutes after 1,1,1-trichloroethane administration by gavage, while blood levels progressively rose when the chemical was infused into the stomach, exceeding levels in the gavage groups after 60–80 minutes (Mortuza et al. 2018).

Absorption from the gastrointestinal tract is more rapid for 1,1,1-trichloroethane given in water than in vegetable oils, because the oils act as a reservoir for the chemical in the gut, so that most of the chemical remains in the oil in the gut until the oil is digested and absorbed (Reitz et al. 1988; RTI 1987).

1,1,1-Trichloroethane is absorbed through human skin. Absorption of 1,1,1-trichloroethane through skin is dependent on phase of media, exposure conditions (i.e., immersion or topical application), skin type, and size of exposed area. Studies involving dermal absorption showed rapid absorption related to the type or condition of skin exposed, duration of exposure, and exposure concentration (Aitio et al. 1984; Poet et al. 2000; Stewart and Dodd 1964). Other studies where exposure is via percutaneous absorption of solvent vapors have also been conducted and found similar rapid absorption occurring (Giardino et al. 1999; Riihimäki and Pfäffli 1978; Wallace et al. 1989). The compound was detected in alveolar air of human volunteers during 30-minute skin absorption experiments with concentration ranges of 0.1–1.0 ppm after thumb immersion, 21.5 ppm after hand immersion, and 0.65 ppm after hand topical application to the undiluted compound (Stewart and Dodd 1964). 1,1,1-Trichloroethane concentrations in blood and alveolar air were 3–4 μg/mL and 2–5 ppm, respectively, immediately following the last of three daily 2-hour exposures of 12.5-cm^2 areas of covered forearm skin in application experiments (Fukabori et al. 1977). A dermal absorption rate of 56 nmol 1,1,1-trichloroethane/minute/cm^2 was calculated for human subjects exposed for 3 minutes to liquid 1,1,1-trichloroethane (neat) on a 3-cm^2 area of forearm skin (Kezic et al. 2001). Less than 0.2% of the available 1,1,1-trichloroethane was absorbed (with an estimated dermal absorption rate ranging from 0.0057 to 0.0069 cm/hour) in humans after a 2-hour hand immersion in a 0.1% (1 g/kg) water solution of 1,1,1-trichloroethane (Poet et al. 2000). The human dermal absorption rate from a 0.75% soil solution was approximately 1/3 of that from water, with an estimated rate of 0.002±0.0005 cm/hour (Poet et al. 2000). Pre-hydration of skin for 2 hours prior to exposure resulted in 2 orders of magnitude higher estimated absorption (0.528 cm/hour), and a greater mass (377 mg) of the amount absorbed (Poet et al. 2000). Another human study on percutaneous absorption of 1,1,1-trichloroethane from aqueous solutions reported 14.9% dermal uptake in volunteers following a 1-hour immersion of their hand and forearm into water containing 100 μg/L 1,1,1-trichloroethane, and estimated a dermal permeability coefficient of 0.167 cm/hour (Fan et al. 2007). Dermal

absorption was 45.7 nmol/minute/cm^2 in mice after 2.92-cm^2 areas of skin were exposed to undiluted compound for 15 minutes under occluded conditions to prevent evaporative loss (Tsuruta 1975). In rats, ≈30% of a 2-mL volume of undiluted 1,1,1-trichloroethane was absorbed by a 3.1-cm^2 area of skin in 24 hours under occluded conditions (Morgan et al. 1991).

Following dermal exposure of rats to 0.1% 1,1,1-trichloroethane in 5 mL of water (5 cm^2 surface area exposed), peak exhaled breath concentrations (Cmax) of ~1,600 ppb were obtained within 1 hour (Poet et al. 2000). The extent of the absorption was dependent on the exposure duration, as 61 and 87% of the applied dose was absorbed after 4 hours and 8 hours of exposure, respectively (Poet et al. 2000). Rat dermal absorption of 0.15±0.006 cm/hour (33%) from non-occluded soil was half of the absorption rate as measured from water (Poet et al. 2000).

Skin provides an excellent barrier against dermal absorption of 1,1,1-trichloroethane vapors. Negligible amounts of chemical vapors are absorbed through heated and moist skin in a dose-dependent manner. After exposure to vapor concentrations ranging from ~1,200 to 4,800 mg/m^3, 25–260 µg/m^3 1,1,1-trichloroethane was exhaled in a linearly dose-dependent manner (Giardino et al. 1999). Dermal uptake from the whole body was approximately 0.1%, while dermal uptake through a forearm and hand, which is 30% of the total body surface area, was approximately 0.031% (Giardino et al. 1999; Riihimäki and Pfäffli 1978). An absorption rate into skin of 0.021 cm/hour and a maximum absorption rate into the blood of 0.005 nmol/hour were reported for volunteers whose forearm and hand were exposed to approximately 38,000 ppm 1,1,1-trichloroethane vapors for 20 minutes (Kezic et al. 2000).

3.1.2 Distribution

No studies were identified regarding the distribution of 1,1,1-trichloroethane to human tissues after inhalation exposure. Nevertheless, 30 autopsies revealed detectable levels of the compound in subcutaneous and renal fat, liver, lung, and muscle (Alles et al. 1988). Additionally, most of absorbed 1,1,1-trichloroethane in humans is rapidly excreted in exhaled air as the unmetabolized parent compound (Caplan et al. 1976; Gamberale and Hultengren 1973).

Animal studies indicate that inhaled 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, with preferential distribution to fatty tissues. 1,1,1-Trichloroethane is rapidly cleared from tissues after exposure ceases (Holmberg et al. 1977; Schumann et al. 1982; Takahara 1986a). Concentrations of 1,1,1-trichloroethane were higher in the liver than in the blood, kidneys, and brain of

mice exposed to 10–10,000 ppm for 0.5–24 hours (fatty tissues were not analyzed separately) (Holmberg et al. 1977). In mice exposed to 1,000 ppm for 1 hour, tissue concentrations immediately after exposure displayed the following order: fat > liver > kidney > spleen = blood > lung = heart = brain (Takahara 1986a). In mice and rats exposed to 150 or 1,500 ppm 1,1,1-trichloroethane for 6 hours, concentrations were much higher (~11–26-fold) in fatty tissue than concentrations in the liver and kidneys immediately following exposure (Schumann et al. 1982). Four hours after the last exposure, male dogs exposed to 10,000 ppm 1,1,1-trichloroethane (weight concentrations) for 3 minutes (4 times at 4-hour intervals) had the following order of wet weight concentrations of 1,1,1-trichloroethane in analyzed organs: abdominal fat > renal fat > brain ≈ liver ≈ kidney ≈ lungs (Katagiri et al. 1997). Experiments in which pregnant mice were exposed by inhalation to 1,1,1-trichloroethane showed that the compound also is distributed to fetuses (Danielsson et al. 1986; Shimada 1988). Following a 1-hour exposure of pregnant mice to 1,000 ppm, concentrations of 1,1,1-trichloroethane in maternal organs, fetuses, and placentas ranked in the following order: fat > blood > kidney > liver > placenta > brain > fetus (Shimada 1988).

No studies were identified regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume, and tissue:blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats (100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987). After a 6 mg/kg gavage-administered dose of an aqueous emulsion of 1,1,1-trichloroethane in rats, the chemical was most rapidly distributed to the liver, with levels in the organ peaking within 5 minutes of administration (Mortuza et al. 2018). Peak levels in blood and tissues were observed approximately 15 minutes post-exposure (Mortuza et al. 2018). The liver exhibited a 2–3-fold higher burden of 1,1,1-trichloroethane than all other non-adipose tissues throughout the 18-hour monitoring period (Mortuza et al. 2018). As 1,1,1-trichloroethane is lipophilic, it heavily accumulated in adipose tissue in rats with a peak concentration 10-fold higher than the peak concentration in the liver, which had the next highest peak concentration (Mortuza et al. 2018). Adipose tissue also exhibited delayed clearance compared with other tissues in the rat (Hajimiragha et al. 1986; Meredith et al. 1989; Monster et al. 1979; Mortuza et al. 2018). Consistent with the conclusion that 1,1,1-trichloroethane is stored and gradually released after repeated exposures in Seki et al. (1975).

3.1.3 Metabolism

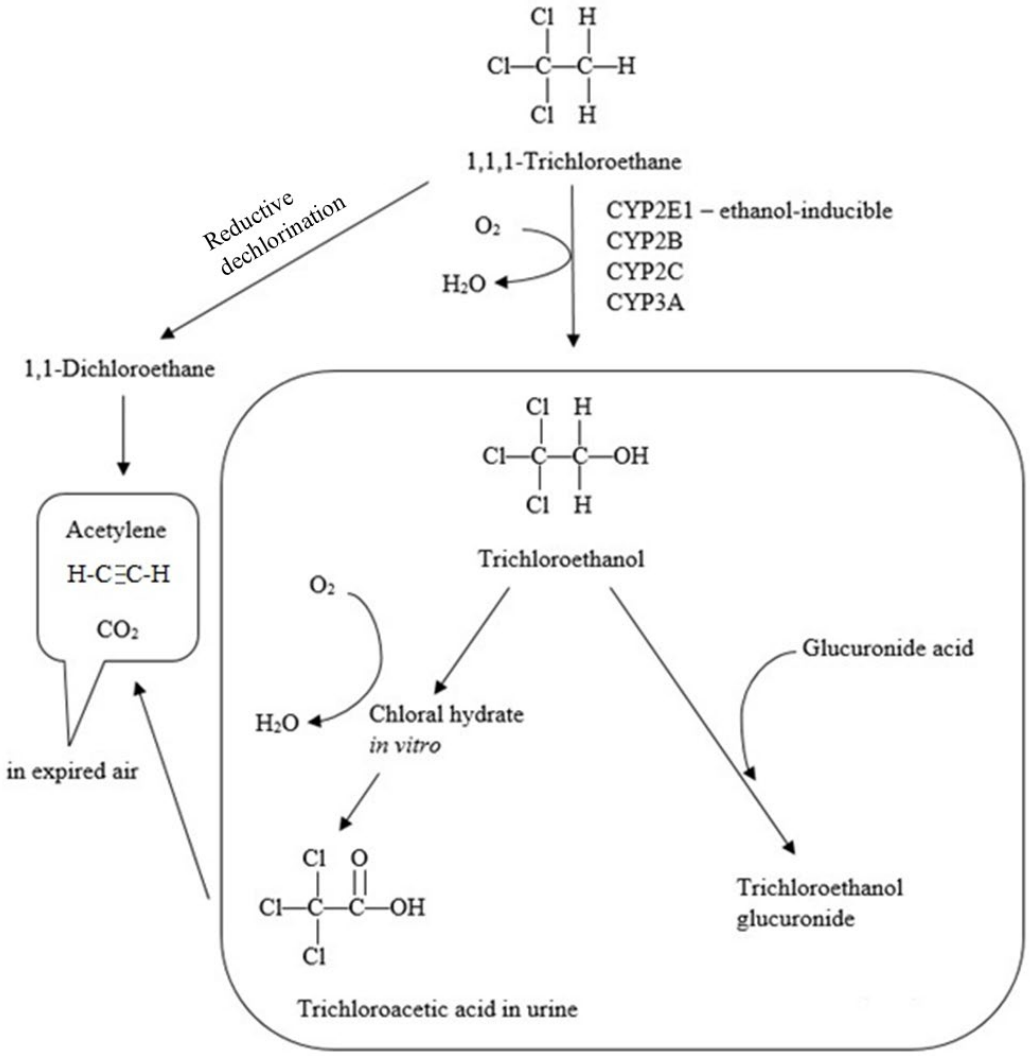
Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. Of the 10% of 1,1,1-trichloroethane that is absorbed, 2–5% is eliminated as trichloroethanol (half-life of 10–27 hours) and 1–2% as trichloroacetic acid (half-life of 70–85 hours) in urine, representing a minor elimination pathway (Humbert and Fernandez 1976; Imbriani et al. 1988; Monster 1986). Human studies have demonstrated that trichloroethanol and trichloroacetic acid are the primary metabolites, with trichloroethanol being the more abundant one of the two (Berode et al. 1990; Kawai et al. 1991; Nolan et al. 1984; Pedrozo and Siqueira 1996; Tomicic et al. 2011).

In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60–80% of the absorbed compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5%, respectively, of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984). The average apparent metabolic clearance of 1,1,1-trichloroethane was estimated at 18.05 mL/minute (Johns et al. 2006).

In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of 14C-labeled compound, 85.1 and 92.3% of the doses (3,000 and 4,000 mg/kg in rats and mice, respectively) were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2–3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dose-dependent, saturable process that represented a minor route of elimination (Schumann et al. 1982; Schumann et al. 1982).

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2, identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982). Figure 3-1 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. *In vitro* reaction mixtures containing rat hepatic microsomes and NADPH oxidize 1,1,1-trichloroethane to trichloroethanol.

Figure 3-1. Metabolic Scheme for 1,1,1-Trichloroethane



1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981; Koizumi et al. 1983).

The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as *in vitro* metabolic products of 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), *in vitro* production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984). Guengerich et al. (1991) concluded that metabolism of 1,1,1-trichloroethane to trichloroethanol occurs primarily by human cytochrome P-450 2E1 (CYP2E1), which is supported by two additional studies (Berode et al. 1990; Johns et al. 2006) that provide indirect evidence for the function of various cytochrome P-450 enzymes in 1,1,1-trichloroethane oxidation. These studies correlated metabolism of 1,1,1-trichloroethane with that of other CYP2E1 substrates and showed that metabolism of 1,1,1-trichloroethane is increased by ethanol consumption. 1,1,1-Trichloroethane is oxidized by one of several cytochrome P-450 enzymes to form trichloroethanol, which subsequently undergoes either oxidation to trichloroacetic acid or glucuronidation to form the corresponding trichloroethanol glucuronide conjugate, TCOG. Both metabolites are recovered in urine, with the majority being trichloroethanol. Most of the metabolic flux is to trichloroethanol rather than trichloroacetic acid (Kawai et al. 1991). Other minor metabolites, including carbon dioxide and acetylene excreted in the exhaled air, have also been described (Tomicic et al. 2011).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to free radical intermediates, including 1,1-dichloroethane (Thompson et al. 1985), and eventually to acetylene (Durk et al. 1992). In these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane (Thompson et al. 1985). The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the *in vitro* and *in vivo* metabolic formation of acetylene (Durk et al. 1992). The reductive metabolic pathway is not indicated in Figure 3-1 because the study authors indicate that it is a minor metabolic pathway.

Repeated exposure of mice and rats to 1,1,1-trichloroethane apparently does not increase the relative importance of metabolism to the *in vivo* disposition of the compound (Schumann et al. 1982), even though another study reported that hepatic microsomes from rats exposed continuously for 10 days to 800 ppm 1,1,1-trichloroethane displayed greater *in vitro* enzymatic activities for 1,1,1-trichloroethane oxidation than microsomes from fresh-air controls (Koizumi et al. 1983). Schumann et al. (1982) found that repeated exposure of rats or mice to 1,500 ppm unlabeled 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, extent of metabolism, or concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm [2–14C]-1,1,1-trichloroethane, compared with age-matched animals subjected to single 6-hour exposures. In general, studies regarding the effects of 1,1,1-trichloroethane on hepatic enzyme induction are inconclusive. Although some studies (Bruckner et al. 2001; Fuller et al. 1970; Koizumi et al. 1983; Lal and Shah 1970) reported that 1,1,1-trichloroethane induced hepatic cytochrome P-450 enzyme levels in rats, others observed no effects (Toftgard et al. 1981; Wang et al. 1996) or inhibitory effects (Nakahama et al. 2000; Savolainen et al. 1977) in rats exposed to 1,1,1-trichloroethane.

3.1.4 Excretion

The major route of elimination of absorbed 1,1,1-trichloroethane is exhaled air, regardless of exposure route. After acute-duration inhalation exposure, most 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity that they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60–80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Rapid exhalation of unchanged 1,1,1-trichloroethane was also observed in humans exposed to 35 or 350 ppm for 6 hours, as 71% of the absorbed 1,1,1-trichloroethane was excreted through exhalation after 1.5 hours and >91% of absorbed 1,1,1-trichloroethane was exhaled as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Stewart et al. (1961) performed controlled human exposures to 1,1,1-trichloroethane vapor and identified an exponential decay curve for the concentration of 1,1,1-trichloroethane in expired air. Additional studies demonstrate the predominance of exhalation of unmetabolized 1,1,1-trichloroethane in the excretion of inhaled or absorbed 1,1,1-trichloroethane (Abe and Wakui 1984; Gill et al. 1991; Hajimiragha et al. 1986; Imbriani et al. 1988; Kawai et al. 1991; Laparé et al. 1995; Mizunuma et al. 1995; Nolan et al. 1984; Seki et al. 1975; Tay et al. 1995; Tomicic et al. 2011). Measurement of 1,1,1-trichloroethane concentration in expired air is the most reliable indicator of exposure (Laparé et al. 1995; Nolan et al. 1984).

Similar observations were made in studies of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982; Schumann et al. 1982), mice (Schumann et al. 1982), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane (Mitoma et al. 1985). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5%, respectively, of the 1,1,1-trichloroethane initially absorbed (Caperos et al. 1982). Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Mizunuma et al. 1995; Seki et al. 1975). After 2 hours of inhalation exposure to 175 ppm 1,1,1-trichloroethane, trichloroethanol was excreted rapidly through human urine, with a recovery of 75% of the total amount of trichloroethanol excreted within 24 hours (Johns et al. 2006). PBPK modeling suggests that urinary excretion of trichloroethanol represents 41% of the total metabolites excreted, while trichloroacetic acid excreted in urine represents 10–20% of the total metabolites (Laparé et al. 1995). The urinary excretion of trichloroethanol and trichloroacetic acid decreased linearly over the 70 hours following exposure once peak concentrations were reached in 3 and 40 hours, respectively (Johns et al. 2006). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10–27 and 70– 85 hours, respectively (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982; Takahara 1986b). The slope of the concentration-time course of 1,1,1-trichloroethane in the chamber air of a closed system in steady state appeared to be constant with respect to amount of chemical injected into

rats, with exposure concentrations ranging from 0.6 to 146 µmol 1,1,1-trichloroethane (Yoshida et al. 1998). This suggests that 1,1,1-trichloroethane was excreted through exhalation proportionally to the amount that was administered to the rats.

Controlled human exposures to approximately 103 ppm 1,1,1-trichloroethane in a 12-m^3 air-conditioned exposure chamber for 6 hours exhibited differences in urinary excretion of trichloroethanol and trichloroacetic acid between men and women, and also differences between women taking hormonal contraceptives and those who were not (Tomicic et al. 2011). However, no differences were observed in the amount of exhaled unchanged 1,1,1-trichloroethane between sexes (Tomicic et al. 2011). Urinary excretion of trichloroethanol throughout the 24 hours after exposure to 1,1,1-trichloroethane was highest in women taking hormonal contraceptive, followed by women not taking hormonal contraceptives, and was lowest in men (Tomicic et al. 2011).

Humans also eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966). The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of 14C-labeled compound, 85.1 and 92.3% of the doses (3,000 and 4,000 mg/kg in rats and mice, respectively) were recovered as unchanged compound in expired air; respective recovery percentages of metabolite fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2, 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in expired air, accounting for >90% of administered doses; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (RTI 1987). Approximately 14.8% of the chemical in venous blood was eliminated during its first pass through the liver and lungs, respectively, after oral administration of 10 mg 1,1,1-trichloroethane/kg in rats (Mortuza et al. 2018). Excretion via the mother's milk does not appear to be significant for 1,1,1-trichloroethane. Approximately 0.04% of an orally administered dose of 1,1,1-trichloroethane was excreted in the 24-hour milk of lactating goats (Hamada and Tanaka 1995).

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route and exhalation of CO_2 and urinary excretion of other metabolites are minor routes. Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimäki and Pfäffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantified in these studies. The concentration of 1,1,1-trichloroethane in expired air can be used as an indicator of dermal uptake of 1,1,1-trichloroethane vapors; however, dermal uptake of vapors is negligible compared with inhalation exposure from vapors (Giardino et al. 1999; Riihimäki and Pfäffli 1978).

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air and 1% was excreted as metabolites in urine (Takahara 1986a). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloroethane, exhalation of radioactivity accounted for 91 and 80% of the administered doses in rats and mice, respectively; only trace amounts of radioactivity remained in the tissues after 24 hours (RTI 1987).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical

descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

There have been many PBPK models developed, some of which were subsequently reconstructed and updated, to describe the amount of 1,1,1-trichloroethane and its metabolites that reach target organs and excretion pathways.

PBPK models developed in Caperos et al. (1982) and Nolan et al. (1984) describe the fate of inhaled 1,1,1-trichloroethane in humans, and both simulate the chemical's absorption, elimination, and excretion through expired air, kinetics of formation, and elimination and the urinary excretion of its metabolites. These models estimate first-order rate constants describing metabolic and urinary elimination of 1,1,1-trichloroethane and its metabolites based on the Fernandez et al. (1977) model for trichloroethylene. Both the Caperos et al. (1982) and the Nolan et al. (1984) models combine the liver compartment, which is a target organ of 1,1,1-trichloroethane metabolism, into the well perfused tissue compartment. The Caperos et al. (1982) model calculates metabolic clearance of 1,1,1-trichloroethane indirectly from data (Humbert and Fernandez 1977) on exposure to trichloroethylene. The Nolan et al. (1984) model describes 1,1,1-trichloroethane concentrations in the expired air and venous blood based on the partition coefficients and metabolism rate constant, which were estimated from data in volunteers who inhaled 35 or 350 ppm of the compound for 6 hours in this study.

Gargas et al. (1986) developed a model based on a four-compartment model that was originally developed for styrene by Ramsey and Andersen (1984), using data obtained from closed-chamber gas uptake studies in rats exposed to 0.2, 1.0, 10, or 210 ppm 1,1,1-trichloroethane. The model describes a chemical exchange compartment (lung), in addition to four other compartments (liver, viscera, muscle/skin, and fat). The model assumes equilibrium between the concentrations in blood leaving the lung and in alveolar air, which is controlled by an experimentally measured blood:air partition coefficient, and the flow-limited tissue uptake of 1,1,1-trichloroethane, by using the experimentally estimated tissue:air partition coefficient. According to the model, 1,1,1-trichloroethane is eliminated through exhalation and exhibits first-order metabolism at a rate constant of 7.8 per hour in the liver.

Reitz et al. (1988) developed a unified PBPK model for 1,1,1-trichloroethane in rats, mice, and humans (based on the previously mentioned styrene model by Ramsey and Andersen [1984]). The model consists of four compartments, including liver, rapidly perfused tissue, slowly perfused tissue, and fat. Tissue volumes and blood and airflow rates employed in the model are listed in Table 3-1. Blood:air and

tissue:air partition coefficients for rats, and blood:air partition coefficients for humans and mice were obtained from Gargas et al. (1986, 1989). Tissue:blood partition coefficients for rats, humans, and mice were calculated by dividing tissue:air partition coefficients for rats, humans, and mice by rat blood:air partition coefficients. Metabolic parameters for the rat (V_{max}, K_m) were derived from rat inhalation exposure data to 150 or 1,500 ppm for 6 hours in Schumann et al. (1982). Uptake of 1,1,1-trichloroethane via bolus gavage was simulated to have a first-order rate constant of 1.25/hour (Reitz et al. 1988).

Table 3-1. Parameters Used in the Physiologically Based Pharmacokinetic Model for 1,1,1-Trichloroethane Developed by Reitz et al. (1988)

	Human	Rat	Mouse
Weights			
Body weight (kg)	83	0.215	0.029
Liver (%)	3.1	4	4
Rapidly perfused (%)	3.7	5	5
Slowly perfused (%)	61.1	75	78
Fat (%)	23.1	7	4
Flows (L/hour)			
Alveolar ventilation	348	5.11	1.26
Cardiac output	348	5.11	1.26
Liver (% cardiac output)	24	24	24
Rapidly perfused (% cardiac output)	49	53	56
Slowly perfused (% cardiac output)	18	18	18
Fat (% cardiac output)	9	5	2
Partition coefficients			
Blood/air[a]	2.53	5.76	10.8
Liver/air[b]	8.6	8.6	8.6
Rapidly perfused/air[b]	8.6	8.6	8.6
Slowly perfused/air[b]	3.15	3.15	3.15
Fat/air[b]	263	263	263
Biochemical constants[c]			
$V_{max}C$	0.419	0.419	0.419
K_m (mg/L)	5.75	5.75	5.75
K_a ($hour^{-1}$) (first-order rate constant for gastrointestinal absorption	–	1.25	–

[a]Gargas et al. (1989).
[b]Fiserova-Bergerova and Diaz (1986).
[c]$V_{max}C$ and K_m were obtained for the rat from the blood level data of Schumann et al. (1982) by computer optimization. $V_{max}C$ is an allometric measure of maximum velocity of metabolism showing the following relationship with maximum enzyme rate: $V_{max} = V_{max}C \times (\text{body weight}) + 0.7$.

Predictions based on the model were compared to observed values for experimentally determined end exposure 1,1,1-trichloroethane blood levels, amount of 1,1,1-trichloroethane metabolized, and concentrations of 1,1,1-trichloroethane in fat or liver of rats and mice following exposure via drinking water or inhalation, and to observed values of the amount of 1,1,1-trichloroethane metabolized in human volunteers following inhalation exposure. Model predictions agreed reasonably well with the empirical observations (Reitz et al. 1988).

Adaptations of the Reitz et al. (1988) model were presented by others (Bogen and Hall 1989; Dallas et al. 1989; DeJongh et al. 1998; Dobrev et al. 2001, 2002; Leung 1992; Poet et al. 2000; Tardif and Charest-Tardif 1999; Yoshida 1993). The predictions of the Dallas et al. (1989), Leung (1992), Yoshida (1993), and DeJongh et al. (1998) models were not validated with experimental data. The Tardif and Charest-Tardif (1999) model simulated blood concentrations in human volunteers during a 4-hour exposure to 400 ppm 1,1,1-trichloroethane.

Bogen and Hall (1989) adapted the Reitz et al. (1988) rat model to gerbils and humans using a scaling factor and added a skin compartment to account for dermal uptake of 1,1,1-trichloroethane for a reference human weighing 70-kg, assuming skin accounted for 6% of the reference body weight.

Dallas et al. (1989) also adapted the Reitz et al. (1988) model to describe the disposition of 1,1,1-trichloroethane in rats following inhalation exposure with the addition of a lung compartment, assuming that the lung:blood partition coefficient was the same as the liver:blood partition coefficient.

Droz et al. (1989a, 1989b) developed a population physiological model for organic solvents, including 1,1,1-trichloroethane (methyl chloroform), based on the Fernandez et al. (1977) PBPK model for trichloroethylene. The chemical-specific distribution parameter values were either obtained directly from an experiment by Droz and Fernandez (1977), as was the case for the blood:gas partition coefficient, or were subsequently derived from the results of this experiment. Pharmacokinetic parameters describing intrinsic metabolic clearance of the chemical were taken from Droz and Fernandez (1977). The metabolite formation and other information about further biotransformation, distribution, and elimination, including metabolic clearance, volumes of distribution, fraction metabolized, and renal clearances, were calculated from Fernandez et al. (1975) and Humbert and Fernandez (1977). The model was used to simulate variability in biological monitoring of solvent exposure of workers at the threshold limit value (TLV) for 8 hours/day, 5 days/week, for 4 and 5 weeks.

Leung (1992) and Yoshida (1993) also adapted the Reitz et al. (1988) model and obtained chemical distributional parameters from the Gargas et al. (1986) model. Michaelis-Menten metabolism, V_{max}, and K_m were scaled allometrically from values in rats (Reitz et al. 1988) for use in the human liver. The Leung (1992) model simulated 1,1,1-trichloroethane concentrations in expired air and blood, as well as concentrations of metabolites of 1,1,1-trichloroethane in urine after human exposure to 350 ppm (occupational exposure limit) for 8 hours/day and 5 days/week, as this represents a typical work schedule. The changes in ventilation and blood flow rates due to exercise were incorporated into the model. The Yoshida (1993) model estimated the steady-state tissue concentrations of 1,1,1-trichloroethane in the Japanese population after daily exposure through inhalation of ambient air and ingestion of drinking water, milk, meat, fish, and vegetation.

Laparé et al. (1995) developed a model to describe 1,1,1-trichloroethane pharmacokinetics in humans after industrial exposure based on data from volunteers exposed to 84.2–175 ppm in a chamber under various scenarios, including rest and workload conditions. The model was built upon previous models with the addition of a gastrointestinal compartment. Tissue:air partition coefficients for lungs, liver, gastrointestinal tract, fat, muscle and skin, and rapidly and slowly perfused tissues were adopted from Fiserova-Bergerova and Diaz (1986). The blood:air partition coefficient was derived empirically through model optimization. The metabolic rate constants of 1,1,1-trichloroethane in the liver with saturable kinetics were derived from Reitz et al. (1988) and the elimination rate constants of metabolites, trichloroethanol and trichloroacetic acid, through metabolism and urinary excretion were obtained by optimizing the model from starting values of Fernandez et al. (1977). The Laparé et al. (1995) model was used to simulate 1,1,1-trichloroethane concentrations in expired air and venous blood, as well as concentrations of urinary metabolites, and was compared with empirical data from Nolan et al. (1984). The model simulations agreed well with experimental data. Modeling results suggested that toxicokinetics of 1,1,1-trichloroethane and its metabolites are increased proportionally with increased exposure duration.

Fisher et al. (1997) modeled the excretion of 1,1,1-trichloroethane (and other volatile organic chemicals) via the breast milk. Model simulations predicted a low degree (<1%) of lactational transfer of 1,1,1-trichloroethane. However, model predictions were not validated with empirical data.

Poet et al. (2000) built upon the Reitz et al. (1988) PBPK model by incorporating a skin compartment to determine the dermal permeability of 1,1,1-trichloroethane in rats and humans, and by incorporating Fick's law, which says that dermal permeability is a function of the permeability constant (K_p, cm/hour),

the area exposed (cm^2), and the concentration gradient across the skin (mg/cm^3). The model was used to estimate the skin permeability coefficient (K_{ps}) for dermal absorption of 1,1,1-trichloroethane in rats from water and soil and in humans from water. K_{ps} in rats from non-occluded soil was predicted to be lower than from water.

The Dobrev et al. (2001, 2002) model, which was adapted from Reitz et al. (1988), evaluated interactions for mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in humans and rats by incorporating terms for various types of competitive metabolism in the liver.

The use of PBPK modeling was explored to establish biological exposure indices. These indices represent the concentration of the chemical or metabolite collected from a worker who has been exposed to an airborne concentration at the American Conference of Governmental Industrial Hygienists (ACGIH) TLV, and for deriving toxicity reference values. The Reitz et al. (1988) model and previously reported values of biochemical parameters were applied in several more studies for such purposes (Leung 1992; Lu et al. 2008; Thomas et al. 1996).

Thomas et al. (1996) paired the Leung (1992) PBPK model with a Monte Carlo simulation to estimate the interindividual variability in the concentrations of 1,1,1-trichloroethane in exhaled breath and urine following industrial exposure, and to compare these results with existing biological exposure indices. The model predictions were further applied to derive the percentage of the occupationally exposed population that were protected based on the current ACGIH threshold limit value. The model estimates suggested that workers were not being adequately protected with the current biological exposure index for end-exhaled air (<10% of the workers were protected); for urinary trichloroacetic acid, half of the workers were protected (Thomas et al. 1996).

Chen et al. (2004) applied a simplified one-compartment model, which handled the entire body as a single compartment by assuming the equilibrium state of the internal chemical concentrations, to estimate interindividual variability in biological exposure indices corresponding to the percentages of protection for workers exposed to TLVs of 1,1,1-trichloroethane.

EPA (2006) explored all available PBPK models published in the literature for 1,1,1-trichloroethane at the time of the report and provided a detailed description of the reconstruction of the models. Based on a thorough evaluation of the model, the Reitz et al. (1988) model was selected for further application in the estimation of internal doses for both humans and rats under a variety of exposure scenarios and

extrapolations across exposure duration, species, and exposure route to support health assessments of 1,1,1-trichloroethane.

Lu et al. (2008) replicated the Gargas et al. (1986) and Reitz et al. (1988) models from the original code and evaluated the two models by comparing their predictions with experimental data in rats and humans. The Reitz et al. (1988) model was selected as the most suitable PBPK model for supporting reference value derivation and further applied in this study for estimation of various internal dose metrics of 1,1,1-trichloroethane and for extrapolations across durations, species, and routes. The model predicted internal dose metrics, including a venous blood concentration of 1.33 mg/L and an area-under-the-curve (AUC) of venous blood concentration of 1.09 mg/L-hour at the end of inhalation exposure to 175 ppm 1,1,1-trichloroethane for 1 hour in humans. The model also back-calculated the external concentrations of continuous exposure at 4, 8, and 24 hours of exposure. The results suggested that blood concentration is a reliable dose metric in duration extrapolation for short term continuous exposure scenarios. Human equivalent concentrations calculated based on average daily AUCs in venous blood were 2-fold higher than those based on average daily AUC concentrations in liver. The study also suggested the potential use of interspecies extrapolation in pharmacokinetics to replace the default pharmacokinetic uncertainty factors in the derivation of the subchronic and chronic inhalation reference concentrations (RfCs).

Valcke and Krishnan (2011a) developed a PBPK model for four volatile organic compounds (VOCs), including benzene, styrene, 1,1,1-trichloroethane, and 1,4-dioxane, based on the Haddad et al. (1996) model in rats, which is a PBPK model solved by a methodology without the use of simulation software. The Valcke and Krishnan (2011a) model assessed the impact of exposure duration and magnitude on the human kinetic adjustment factor, which is a data-derived, chemical-specific adjustment factor for interindividual variability in toxicokinetics, for adults as well as several sensitive subpopulations including neonates (0–30 days), toddlers (1–3 years), and pregnant women. These sensitive subpopulations were assessed to further investigate human interindividual variability in the toxicokinetics of the chemical. The model, which was originally comprised of five compartments in Haddad et al. (1996), including gas exchange, liver, fat, highly perfused, and rest of the body when applied to the general population, was complemented with the compartments of placenta and fetus for pregnant women and neonates. Chemical-specific parameters for 1,1,1-trichloroethane were adapted from Lu et al. (2008) (which was adapted from Reitz et al. 1988), except for the placenta:blood partition coefficients, which were calculated using placenta composition data from Klingler et al. (2003) and Poulin and Krishnan (1995). Physiological parameters originally taken from Haddad et al. (2006) were slightly modified by the study authors' previous work (Valcke and Krishnan 2011b) to allow for the calculation of

physiological parameters as a function of four determinants: body weight, height, age, and sex. The model includes variability terms as multipliers of the calculated physiological parameters for a given set of body weight and height data (Valcke and Krishnan 2011a). The model predicted target dose metrics such as maximum blood concentration and amount metabolized/L liver/24 hours in adults, neonates, toddlers, and pregnant women following various scenarios of inhalation exposure to 1,1,1-trichloroethane. Neonates were predicted to be the most sensitive subpopulation, followed by toddlers, and then general population adults. Valcke and Krishnan (2011a) ultimately found that the human kinetic adjustment factor of up to 2.1 that was derived from the predicted amount of metabolized 1,1,1-trichloroethane was within the default uncertainty factor, and was 2-fold higher than the human kinetic adjustment factor derived from variability in the maximum concentration.

Nong and Krishnan (2007) reconstructed algorithms into steady-state conditions associated with inhalation exposures to 1,1,1-trichloroethane from PBPK models (Leung 1992; Thomas et al. 1996) to estimate an interindividual variability factor of pharmacokinetics to allow for the computation of upper and lower bounds of a probability distribution. The values and probability distributions of input parameters of the PBPK models, including alveolar ventilation, hepatic blood flow, and blood:air partition coefficient, were obtained from Price et al. (2003) and Thomas et al. (1996). Intrinsic clearance of metabolism was calculated as a ratio of maximal metabolic velocity (V_{max}) and Michaelis constant (K_m) (Rane et al. 1977). The interindividual variability factor in pharmacokinetics for 1,1,1-trichloroethane based on the probability-bounds of arterial blood concentration and the rate of metabolism were 1.18 and 1.24, respectively, using probability distribution-defined inputs.

Boogaard et al. (2011) illustrated the derivation of biomonitoring equivalent values corresponding to risk assessment-based derived no-effect levels, using an approach of applying steady-state solutions to a generic physiologically based toxicokinetic (PBTK) model for VOCs developed by Chiu and White (2006) that requires only three chemical-specific parameters: V_{max}, K_m, and the blood:air partition coefficient. The study authors estimated a steady-state blood concentration of 317 µg/L 1,1,1-trichloroethane in humans associated with chronic-duration inhalation exposure to air concentrations of 75 mg/m^3 using chemical-specific parameters for 1,1,1-trichloroethane. The adjusted biomonitoring equivalent corresponding to a risk assessment-based derived no-effect level was estimated at 100 µg/L for the general population (Boogaard et al. 2011).

3.1.6 Animal-to-Human Extrapolations

Species-specific differences in pharmacokinetic properties of inhaled 1,1,1-trichloroethane have been demonstrated. Nolan et al. (1984) reported 2.5- and 3-fold greater absorption in rats and mice, respectively, relative to humans following equivalent inhalation exposures. Measured blood levels in the rats and mice were 3.5- and 17.3-fold higher than humans, and the amount of 1,1,1-trichloroethane metabolized was 4.3-fold higher in rats and 11.4-fold higher in mice than humans. These results indicate that humans would have to be exposed to 1,1,1-trichloroethane vapor concentrations much higher than those of rats and mice in order to achieve similar blood levels. Although pharmacokinetic differences are readily apparent, species-specific differences in pharmacodynamics have not been elucidated. Note that knowledge of species differences and animal-to-human extrapolations is challenging due to lack of direct comparability between biological processes.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,1,1-trichloroethane are discussed in Section 5.7, Populations with Potentially High Exposures.

No information was located regarding potential age-related differences in susceptibility to 1,1,1-trichloroethane in humans. Delays in developmental milestones (pinnae detachment, incisor eruption, and eye opening) and impaired performance in neurobehavior tests were noted in mouse pups of dams exposed to 1,1,1-trichloroethane during later stages of gestation at levels that did not result in apparent maternal

toxicity (Jones et al. 1996). These results suggest that developing organisms may be more susceptible than adults to the toxic effects of 1,1,1-trichloroethane.

Differences in the urinary excretion of trichloroethanol and trichloroacetic acid in humans were observed based on sex and sexual hormone levels after controlled human exposures to inhalation of 103 ppm 1,1,1-trichloroethane for 6 hours (Tomicic et al. 2011). The excretion of trichloroethanol in urine was quantified in men and women was 5.42±2.19 mg/g creatinine and 3.77±1.24 mg/g creatinine, respectively.

Limited data from animal studies (Woolverton and Balster 1981) indicate that alcohol drinkers may be more susceptible to the acute neurobehavioral effects of 1,1,1-trichloroethane. Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 enzymes involved in the activation of these compounds to intermediate hepatotoxic metabolites. Available animal studies (Cornish and Adefuin 1966; Klaassen and Plaa 1966, 1967) have not demonstrated that ethanol ingestion alone will potentiate the hepatotoxicity of 1,1,1-trichloroethane. Furthermore, evidence indicates that ethanol does not cause 1,1,1-trichloroethane and carbon tetrachloride to interact synergistically to produce hepatotoxic effects, although such an interaction has been demonstrated for ethanol, carbon tetrachloride, and chloroform (Ikatsu and Nakajima 1992).

Diabetics consistently in a state of ketosis may be more susceptible to the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to a potentiation from increased ketone levels in the body (Plaa 1986, 1988). Animal studies indicate that the ketone potentiation of the hepatotoxicity of chlorinated alkanes involves an enhancement of the metabolic production of hepatotoxic intermediate metabolites (Plaa 1986, 1988). Available data, however, indicate that ketones do not appreciably potentiate the hepatotoxicity of 1,1,1-trichloroethane (Plaa 1986, 1988). Thus, diabetics in a state of ketosis are not likely to be more susceptible to the hepatotoxicity of 1,1,1-trichloroethane than the population at large.

Because 1,1,1-trichloroethane is associated with some cardiovascular effects (see Section 2.5), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,1,1-trichloroethane from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,1,1-trichloroethane are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,1,1-trichloroethane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine.

A significant correlation was observed between ambient concentrations of 1,1,1-trichloroethane and levels of the chemical in expired air of the general population living in various U.S. locations during various seasons (Hartwell et al. 1987; Wallace et al. 1982, 1984, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane were 4.9 mg/g creatinine. At 5–15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of people with no characterized exposure sources was 0.0002 mg/L (range <0.0001–0.0034 mg/L) (Hajimiragha et al. 1986). This suggests that levels of 1,1,1-trichloroethane in blood, urine, and expired air may be reliable biomarkers of exposure to 1,1,1-trichloroethane. The National Health and Nutrition Examination Survey (NHANES) reported that 1,1,1-trichloroethane levels in the blood in the general population were typically less than the limit of detection, but occasionally were detectable in the low ppb range (0.0071–2.89 µg/L) in 2011–2018 (CDC 2022).

Levels of metabolites of 1,1,1-trichloroethane, trichloroethanol, and trichloroacetic acid, have also been quantified in the blood, expired air, and urine. Immediately following exposure, urine levels of 1,1,1-trichloroethane and trichloroacetic acid in workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week were 4.9 and 2.5 mg/g creatinine, respectively (Monster 1986). At 5–15 minutes after exposure, blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively (Monster 1986). For comparison, the baseline blood level of trichloroacetic acid has been measured at 0.0214 mg/L (Hajimiragha et al. 1986). Creatinine adjusted urinary trichloroacetic acid was significantly correlated with blood 1,1,1-trichloroethane in a reference population from the Third NHANES (1988–

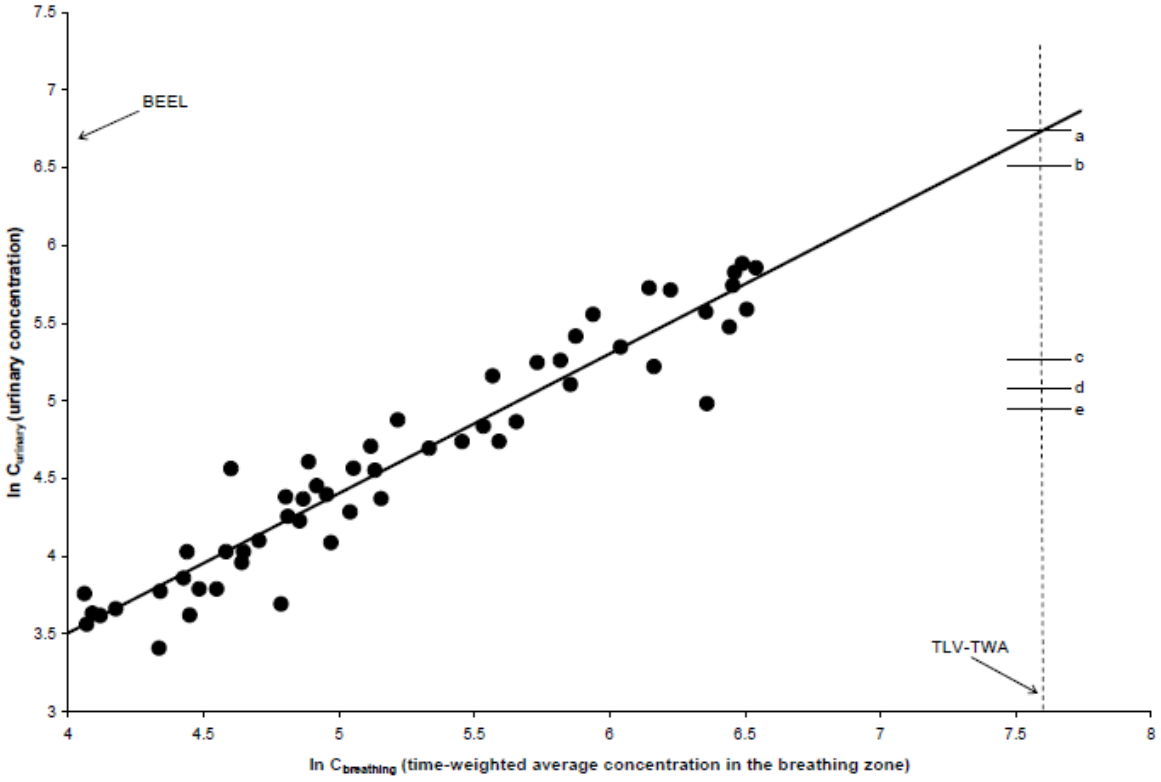
1994) (Calafat et al. 2003). This suggests that levels of the 1,1,1-trichloroethane metabolites of trichloroethanol and trichloroacetic acid in blood and urine may also be effective biomarkers of exposure to 1,1,1-trichloroethane. However, the appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure because of the relatively long half-life of trichloroacetic acid.

Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels and with 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Mizunuma et al. 1995; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 3-2, which show this linear relationship between ambient concentrations of 1,1,1-trichloroethane and urinary concentrations of 1,1,1-trichloroethane.

Monster (1986) proposed that the best method for estimating occupational exposure to 1,1,1-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays. Results of Mizunuma et al. (1995) indicated that urinary levels of 1,1,1-trichloroethane (as parent compound) were more closely correlated to 1,1,1-trichloroethane in the ambient air of a group of 50 solvent workers than the major urinary metabolites, trichloroethanol and trichloroacetic acid. Among four adult volunteers (two males and two females) exposed to several different concentrations of 1,1,1-trichloroethane vapors for various exposure durations, levels of parent compound in alveolar air and blood were more closely correlated with exposure level than urinary levels of parent compound or 1,1,1-trichloroethane metabolites (Laparé et al. 1995).

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites, trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961).

Figure 3-2. Scatter Diagram Relating TWA of Environmental Concentration and Urinary Concentration of 1,1,1-Trichloroethane in Exposed Workers



Scatter diagram relating the time-weighted average (TWA) of the environmental concentration (in the breathing zone) ($C_{breathing}$) and the urinary concentration ($C_{urinary}$) of 1,1,1-trichloroethane in the exposed workers (Experiment II). The regression line ($C_{urinary}$=0.45xCbreathing+12.6; r=0.95; N=60) is also drawn. The letters appearing on the dotted line (x-axis on the far right) represent the following: a = $C_{urinary}$ value at $C_{breathing}$=1,900 mg/m^3 (threshold limit value [TLV]-TWA); b = 95% lower confidence limit = biological exposure limit; c = hypothetical value of $C_{urinary}$ in an occupationally exposed subject; d = one-sided upper confidence limit (at 95%) of $C_{urinary}$ one-sided lower confidence limit (at 95%) of $C_{urinary}$; and e = one-sided confidence limit (at 95%) of $C_{urinary}$. Classification system: 1 d<b (or d/b<1) = compliance exposure 2 e>b (or e/b>1) = noncompliance exposure 3 any individual that cannot be classified in 1 or 2 = possible overexposure.

The $C_{breathing}$ and $C_{urinary}$ values are shown in ln numbers to allow all data in a same diagram. The TLV-TWA is 19,900 mg/m^3 (anti-ln 7.549). The biological equivalent exposure limit (BEEL) is 805 µ/L (anti-ln 6.690).

Source: Imbriani et al. 1988

3.3.2 Biomarkers of Effect

The central nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered electroencephalogram recordings, ataxia, and anesthesia have been observed in humans after acute-duration exposure (Mackay et al. 1987; Muttray et al. 2000; NIOSH 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been

noted (Cohen and Frank 1994; Croquet et al. 2003; Stewart et al. 1961; Texter et al. 1979). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute- and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value as biomarkers, since many other lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effect caused by 1,1,1-trichloroethane were found in the literature.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Although there are no reports of chemical interactions in toxicity of 1,1,1-trichloroethane in humans, several animal studies have identified possible interactions between this and other chemicals.

Ethanol, when given orally to mice at doses of 0.125–2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ~200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (ALT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (ALT or AST), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Cornish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce CYP2E1 (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (ALT, AST, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic effects of cytotoxic haloalkanes. In contrast, co-exposure of ethanol-treated rats to 10 ppm carbon

tetrachloride and 10–50 ppm chloroform produced liver damage that was greater than the additive effects of exposure to each component alone; this synergistic interaction was not observed in rats fed a diet without ethanol (Ikatsu and Nakajima 1992). The results, however, provide no evidence for a synergistic interaction between carbon tetrachloride and 1,1,1-trichloroethane that would enhance the hepatotoxicity of either compound. In experiments with isolated rat hepatocytes, concomitant exposure to chloroform, but not co-exposure to 1,1,1-trichloroethane, potentiated carbon tetrachloride-induced lipid peroxidation (Kefalas and Stacey 1991).

A review study by Pohl and Scinicariello (2011) concluded that 1,1,1-trichloroethane is not expected to enhance the hepatotoxicity of trichloroethylene via cytochrome P-450 induction as the isozymes involved in the metabolism of both chemicals are similar. Additionally, the mixture of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene are not expected to influence each other's toxicity based on their metabolism. This mixture is the most frequently occurring mixture of four volatile organic chemicals and has been found in several NPL sites. A review of vapor intrusion sites assessed by ATSDR found the sites with the three highest concentrations of 1,1,1-trichloroethane in groundwater also contained elevated concentrations of 1,1-dichloroethane and trichloroethylene (ATSDR 2005a, 2005b, 2006; Burk and Zarus 2013). Although exposure to each of the chemicals individually produces similar health effects, limited evidence on the joint toxicity of the chemicals suggests additive interactions on neurological impairment and liver and kidney effects (ATSDR 2004). Administration of a liquid diet containing 2 g/day ethanol for 3 weeks increased the *in vitro* and *in vivo* metabolism of 1,1,1-trichloroethane in rats at all concentrations of exposure to 50, 100, 500, and 1,000 ppm 1,1,1-trichloroethane via inhalation for 6 hours (Kaneko et al. 1994). The enhanced metabolism of 1,1,1-trichloroethane shown by an increase in the urinary excretion of its metabolites indicates that enzymes induced by ethanol affected the metabolism of 1,1,1-trichloroethane *in vivo* at any exposure level. Tetrachloroethylene inhibited the rate of urinary excretion of a 1,1,1-trichloroethane metabolite in rats exposed via inhalation to a mixture containing 350 ppm 1,1,1-trichloroethane and 100 ppm tetrachloroethylene (Koizumi et al. 1982).

Ketones (organic compounds containing a carbonyl group =C=O bonded to two hydrocarbon groups) and ketogenic substances (i.e., substances metabolized to ketones or that produce ketosis in the body) potentiate the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane (Plaa 1988). Although the mechanism of this potentiation is not fully understood, Plaa (1988) proposed enhanced bioactivation of the toxicant through cytochrome P-450 induction. Studies with mice, however, found that treatment with acetone or isopropanol (which is metabolized to acetone) did not enhance the hepatotoxicity of 1,1,1-trichloroethane, but enhanced the

threshold doses of chloroform, 1,1,2-trichloroethane, and trichloroethylene to elevate ALT (Traiger and Plaa 1974). Single intraperitoneal doses of 1,1,1-trichloroethane (1.0 mL/kg) did not produce liver damage (assayed either as elevation in ALT or in concentrations of liver triglycerides) in control mice or in mice with alloxan-induced diabetes (i.e., that were in a state of ketosis) (Hanasono et al. 1975). Other studies examining the influence of agents that enhance cytochrome P-450 metabolism have provided mixed results. The cytochrome P-450 mixed-function oxidase inducer, phenobarbital, enhanced the hepatotoxicity of 1,1,1-trichloroethane in the rat study by Carlson (1973) but not in that by Cornish et al. (1973). In general, the available data suggest that ketones, ketogenic substances, or cytochrome P-450 inducers will not potentiate 1,1,1-trichloroethane hepatotoxicity.

Concurrent injections of nicotine potentiate the lethality produced by intraperitoneal injection of 1,1,1-trichloroethane in mice (Priestly and Plaa 1976). Although no explanation has been given for the effect of nicotine, the study authors suggested that stimulation of the sympathetic nervous system and release of epinephrine from the adrenal medulla might enhance cardiac arrhythmias.

Lal and Shah (1970) found that administration of 1,1,1-trichloroethane reduced the hypnosis effects of hexobarbital in male mice. The study found that a short-term inhalation exposure to 1,1,1-trichloroethane at 2,972 ppm (8–96 hours) reduced hexobarbital sleeping time by 50%. The study authors speculated that this decrease in hexobarbital-induced hypnosis was due to 1,1,1-trichloroethane stimulating the liver to better oxidize the hexobarbital, rather than causing a change in the sensitivity of the central nervous system to the depressant.

Human exposure to concentrations of 400 ppm 1,1,1-trichloroethane and 200 ppm m-xylene following 4 hours of inhalation and pharmacokinetic analysis at steady state using PBPK modeling illustrated that combined exposures to the chemicals did not affect 1,1,1-trichloroethane blood levels, but significantly reduced the formation and excretion of its metabolites, trichloroethanol and trichloroacetic acid (Tardif and Charest-Tardif 1999). Ethanol consumption, which was administered at 0.35 g/kg body weight in moderate drinkers 7 days prior to exposure to 175 ppm 1,1,1-trichloroethane via inhalation for 2 hours on two separate occasions significantly increased the apparent metabolic clearance of the compound by 25.4% on average (Johns et al. 2006).

A PBPK model developed by Dobrev et al. (2001, 2002) evaluated interactions of mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane in humans and rats by incorporating terms for various types of competitive metabolism in the liver. The simulated peak 1,1,1-trichloroethane

blood level was increased by 42% following co-exposure to 2,000 ppm concentrations of perchloroethylene and 1,1,1-trichloroethane, while the total 1,1,1-trichloroethane metabolites generated were decreased by 84% compared to those after a single exposure to 50 ppm of 1,1,1-trichloroethane only (Dobrev et al. 2002).