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Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans ☆

Weihsueh A. Chiu [a,*], Gary L. Ginsberg [b]

[a] National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC 20460, USA
[b] Connecticut Department of Public Health, Hartford, CT 06106, USA

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ABSTRACT

This article reports on the development of a "harmonized" PBPK model for the toxicokinetics of perchloroethylene (tetrachloroethylene or perc) in mice, rats, and humans that includes both oxidation and glutathione (GSH) conjugation of perc, the internal kinetics of the oxidative metabolite trichloroacetic acid (TCA), and the urinary excretion kinetics of the GSH conjugation metabolites N-Acetylated trichlorovinyl cysteine and dichloroacetic acid. The model utilizes a wider range of *in vitro* and *in vivo* data than any previous analysis alone, with *in vitro* data used for initial, or "baseline," parameter estimates, and *in vivo* datasets separated into those used for "calibration" and those used for "evaluation." Parameter calibration utilizes a limited Bayesian analysis involving flat priors and making inferences only using posterior modes obtained via Markov chain Monte Carlo (MCMC). As expected, the major route of elimination of absorbed perc is predicted to be exhalation as parent compound, with metabolism accounting for less than 20% of intake except in the case of mice exposed orally, in which metabolism is predicted to be slightly over 50% at lower exposures. In all three species, the concentration of perc in blood, the extent of perc oxidation, and the amount of TCA production is well-estimated, with residual uncertainties of ~2-fold. However, the resulting range of estimates for the amount of GSH conjugation is quite wide in humans (~3000-fold) and mice (~60-fold). While even high-end estimates of GSH conjugation in mice are lower than estimates of oxidation, in humans the estimated rates range from much lower to much higher than rates for perc oxidation. It is unclear to what extent this range reflects uncertainty, variability, or a combination. Importantly, by separating total perc metabolism into separate oxidative and conjugative pathways, an approach also recommended in a recent National Research Council review, this analysis reconciles the disparity between those previously published PBPK models that concluded low perc metabolism in humans and those that predicted high perc metabolism in humans. In essence, both conclusions are consistent with the data if augmented with some additional qualifications: in humans, oxidative metabolism is low, while GSH conjugation metabolism may be high or low, with uncertainty and/or interindividual variability spanning three orders of magnitude. More direct data on the internal kinetics of perc GSH conjugation, such as trichlorovinyl glutathione or tricholorvinyl cysteine in blood and/or tissues, would be needed to better characterize the uncertainty and variability in GSH conjugation in humans.

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Introduction

Perchloroethylene (tetrachloroethylene or perc) is a volatile organic solvent that has had widespread commercial and industrial use, particularly for commercial dry cleaning, and to a lesser extent in degreasing of metal parts and as a chemical intermediate. Perc is also a common environmental contaminant at hazardous waste sites, in groundwater, and in ambient and indoor air. Like the related solvent trichloroethylene (TCE), perc is a dense nonaqueous-phase liquid and is particularly difficult to remediate once it has entered groundwater.

Understanding perc toxicokinetics is critical to both the qualitative and quantitative assessment of human health risks from environmental exposures and continues to be the subject of active research (Chiu et al., 2007; Sweeney et al., 2009; Boyes et al., 2009). A number of the neurotoxic effects of perc appear well correlated with parent compound concentrations at the target site (Bushnell et al., 2005), so characterizing perc blood or tissue concentrations can aid in

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* Corresponding author at: Express Delivery Address: U.S. Environmental Protection Agency — 8623P, Two Potomac Yard (North Building), 2733 South Crystal Drive, Arlington, VA 22202, USA. Fax: +1 703 347 8692.
E-mail addresses: chiu.weihsueh@epa.gov (W.A. Chiu), gary.ginsberg@ct.gov (G.L. Ginsberg).

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performing risk assessment-related extrapolations, such as between rodents and humans or between exposure routes. In addition, understanding perc metabolism is especially important toxicologically because specific metabolites or metabolic pathways are associated with a number of observed toxic endpoints.

Perc and its metabolites trichloroacetic acid (TCA) and dichloroacetic acid (DCA) cause a number of similar effects in the liver of laboratory animals, including hepatomegaly in rats and mice and hepatocarcinogenicity in multiple strains and both sexes of mice but not in rats (NCI, 1977; NTP, 1986; JISA, 1993; DeAngelo et al., 1999, 2008; Pereira, 1996). As with TCE (Evans et al., 2009; Buben and O'Flaherty, 1985), it has been noted that perc-induced hepatomegaly in mice is better correlated with oxidative metabolism than with the parent compound (Buben and O'Flaherty, 1985). Thus, it has been hypothesized that hepatotoxicity from perc exposure is a result of oxidative metabolism. Under this hypothesis, the lack of apparent hepatocarcinogenicity in rats as compared to the clear hepatocarcinogenicity in mice may partially be explained by differences in perc oxidative metabolism and/or internal doses of TCA, which seem to correlate with sensitivity. However, TCA itself appears to be a more potent hepatocarcinogen in mice than rats, a difference which is as yet not fully explained.

In the kidney, perc causes tubular toxicity in both mice and rats, and is associated in one study with small increases in the incidences of kidney tumors rats (NTP, 1986; JISA, 1993). These effects are thought to be associated with the perc metabolism by glutathione (GSH) conjugation, based on the production in the kidney of nephrotoxic and genotoxic metabolites from this pathway (Lash and Parker, 2001). It has been hypothesized that quantifying differences in the extent of GSH conjugation across species can help to explain the observed species differences in carcinogenicity. However, attempts to make such inferences based on *in vitro* data have been inconsistent (e.g., Green et al., 1990; Dekant et al., 1998; Lash et al., 1998), and no attempt as yet has been made to incorporate GSH conjugation in a PBPK model.

It is less clear to what extent other effects of perc in rodents, such as brain gliomas (NTP, 1986) or mononuclear cell leukemias (JISA, 1993) in rats, are a result of perc itself and/or one or more metabolites. In terms of epidemiologic data, some studies suggest that the kidney and liver may be targets of perc toxicity in humans (Gennari et al., 1992; Mutti et al., 1992; Brodkin et al., 1995), but the available data are too limited to make any definitive conclusions. A recently updated occupational cohort study reported a new finding of increased incidence of end-stage renal disease among dry cleaning workers, further supporting a role for perc in kidney toxicity (Calvert et al., 2010). However, the strongest and most consistent epidemiologic evidence remains that for neurotoxic effects (Altmann et al., 1995; Echeverria et al., 1995; Ferroni et al., 1992; Schreiber et al., 2002; Seeber, 1989).

A simplified metabolism scheme for perc is shown in Fig. 1. Briefly, as reviewed by Lash and Parker (2001), metabolism of perc occurs through two main irreversible pathways: oxidation via the microsomal mixed-function oxidase system (i.e., cytochrome P450s) and conjugation with GSH by glutathione *S*-transferases. The primary

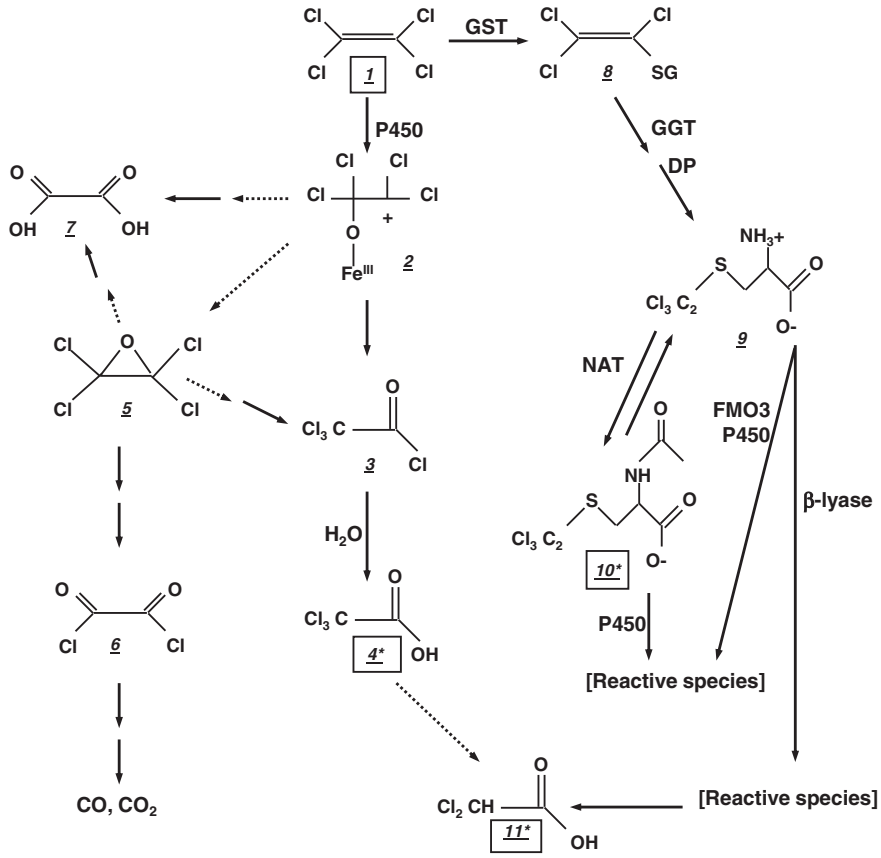

Fig. 1. Simplified perchloroethylene (perc) metabolism scheme. *1*, tetrachloroethylene; *2*, tetrachloroethylene-Fe–O intermediate; *3*, trichloroacetyl chloride; *4*, trichloroacetic acid; *5*, tetrachloroethylene oxide; *6*, ethandioyl dichloride; *7*, oxalic acid; *8*, S-(1,2,2-trichlorovinyl) glutathione (TCVG); *9* S-(1,2,2-trichlorovinyl)-L-cysteine (TCVC); *10*, N-acetyl trichlorovinyl cysteine (NAcTCVC); *11*, dichloroacetic acid. Enzymes: cytochrome P450 (P450), glutathione-S transferase (GST), gamma-glutamyltransferase (GGT), dipeptidase (DP), beta-lyase (β-lyase), flavin mono-oxygenase-3 (FMO3), N-Acetyl transferase (NAT). Metabolites marked with asterisk (*) are known urinary metabolites. Dotted lines indicate hypothesized or quantitatively minor pathways. Boxes indicate chemicals/metabolites included explicitly in the PBPK model (see Fig. 3).