

A Comparative Study of the Pharmacokinetics of Carbon Tetrachloride in the Rat following Repeated Inhalation Exposures of 8 and 11.5 hr/day¹

D. J. PAUSTENBACH,² G. P. CARLSON,* J. E. CHRISTIAN, AND G. S. BORN

*School of Pharmacy and Pharmacal Sciences, Environmental Toxicology Program; and *Department of Pharmacology and Toxicology, Purdue University, West Lafayette, Indiana 47907*

A Comparative Study of the Pharmacokinetics of Carbon Tetrachloride in the Rat following Repeated Inhalation Exposures of 8 and 11.5 hr/day. PAUSTENBACH, D. J., CARLSON, G. P., CHRISTIAN, J. E., AND BORN, G. S. (1986). *Fundam. Appl. Toxicol.* 6, 484-497. To evaluate whether exposure to inhaled vapors for periods longer than 8 hr/day could affect the rates and routes of elimination, male Sprague-Dawley rats were repeatedly exposed to 100 ppm of radio-labeled carbon tetrachloride (¹⁴CCL₄) in a closed-loop chamber. One group was exposed for 8 hr/day for 5 days and another group for 11.5 hr/day for 4 days. Two other groups were exposed for either 8 hr/day for 10 of 12 consecutive days or 11.5 hr/day for 7 of 10 days. The elimination of ¹⁴C activity was measured in the expired air, urine, and feces for up to 100 hr following exposure and the pharmacokinetic parameters were determined. Following 2 weeks of exposure to the 8-hr/day schedule, ¹⁴CCL₄ in the breath and ¹⁴C activity in the feces comprised 45 and 48% of the total ¹⁴C excreted, respectively. Following 2 weeks of exposure to the 11.5-hr/day schedule, the values were 32 and 62%, respectively, indicating that repeated exposure to the longer schedule altered the route of elimination of CCL₄. Regardless of the period of exposure, less than 8% of the inhaled ¹⁴CCL₄ was excreted in the urine and less than 2% was exhaled in the breath as the ¹⁴CO₂ metabolite. Approximately 97-98% of the ¹⁴C activity in the expired air was ¹⁴CCL₄. The quantities of ¹⁴C noted in the feces and urine suggest that more than 60% of the inhaled CCL₄ was metabolized. Elimination of ¹⁴CCL₄ and ¹⁴CO₂ in the breath followed a two-compartment, first-order pharmacokinetic model ($r^2 = 0.98$). For rats exposed 8 hr/day and 11.5 hr/day for 2 weeks, the average half-lives for elimination of ¹⁴CCL₄ in the breath for the fast (α) and slow (β) phases averaged 96 and 455 min, and 89 and 568 min, respectively. The average α and β half-lives for elimination of ¹⁴CO₂ in the breath of rats exposed to the 11.5-hr/day schedule were 455 and 1824 min, and these were significantly longer than for the 8-hr/day groups, 305 and 829 min. The longer half-lives of elimination for ¹⁴CO₂ and ¹⁴CCL₄ which were observed for the groups exposed to the 11.5-hr/day schedule suggest that the 3.5 additional hr of daily exposure places a relatively greater percentage of the absorbed dose into poorly perfused lipophilic depots such as the fat. These results indicate that modest changes in exposure regimen can influence the rate and route of elimination of certain chemicals. Furthermore, since the rat more rapidly metabolizes and eliminates CCL₄ than man, workers exposed 11.5 hr/day or longer can be expected to store relatively larger quantities of CCL₄ in fat and have higher peak blood levels of CCL₄ than that indicated by these results. This study lends support to published recommendations to adjust occupational exposure limits for substances with half-lives between 4 and 200 hr whenever persons will be exposed during work schedules markedly longer than 8 hr/day to assure them the same margin of safety from adverse effects as those who work typical 8-hr/day schedules.