

A linear systems approach to analyzing the pharmacokinetics of carbon tetrachloride in the rat following repeated exposures of 8 and 11.5 h/day

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Abstract. Ten- and 12-h workdays are relatively common in the chemical and other non-labor intensive industries both in the United States and Europe. Based on pharmacokinetic principles, persons who work 10–12 h shifts and are exposed to chemicals with a terminal half-life between 5 and 200 h will absorb a larger quantity of the toxicant or have higher peak blood levels than persons who work 8-h shifts. To evaluate the effects of exposure duration and repeated exposure on the elimination of carbon tetrachloride (CCl₄), rats were repeatedly exposed to 100 ppm ¹⁴CCl₄ for either 8 or 11.5 h/day. Pharmacokinetic equations which describe the plasma concentration and pulmonary elimination during and following single and repeated inhalation exposures were developed. These equations are based on a diffusional type of input function and a linear systems analysis approach. They can be used to make predictions of the cumulation of toxicant following repeated exposure, the relative change in the plasma level following multiple exposures, and the steady-state plasma level based only on the elimination of the chemical in the breath. The pharmacokinetic analysis indicated that rats repeatedly exposed to 100 ppm CCl₄ for 11.5 h/day for 4 days per week, or 8 h/day for 5 days per week, will not have increasing plasma levels. The analysis also predicted no significant difference in the peak plasma concentration of CCl₄ between the 8 and 11.5 h/day schedules following either 1 or 2 weeks of exposure. Due to rapid pulmonary elimination by the rat, the steady state plasma level of CCl₄ was reached after only three consecutive exposures for both schedules. The alpha and beta half-lives ($\bar{x} \pm \text{SE}$) of pulmonary elimination for the 8 h/day group were 84 ± 9 min and 400 ± 32 min, respectively. The half-lives for the 11.5 h group were 91 ± 6 min and 496 ± 32 min, indicating that the beta phase half-life was significantly longer than that of the 8-h group. This observation, coupled with the tissue distribution data (Paustenbach et al. 1986), suggests that during the longer exposure period a greater fraction of CCl₄ is placed in the poorly perfused tissues like fat, thus altering the time-course of elimination in the breath. A general formula for adjusting TLVs for unusually long work schedules is also developed and presented.