

Adjusting Exposure Limits for Long and Short Exposure Periods Using A Physiological Pharmacokinetic Model*

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The rationale for adjusting occupational exposure limits for unusual work schedules is to assure, as much as possible, that persons on these schedules are placed at no greater risk of injury or discomfort than persons who work a standard 8 hr/day, 40 hr/week. For most systemic toxicants, the risk index upon which the adjustments are made will be either peak blood concentration or integrated tissue dose, depending on that chemical's presumed mechanism of toxicity. Over the past ten years, at least four different models have been proposed for adjusting exposure limits for unusually short and long work schedules. This paper advocates use of a physiologically-based pharmacokinetic (PB-PK) model for determining adjustment factors for unusual exposure schedules, an approach that should be more accurate than those proposed previously. The PB-PK model requires data on the blood:air and tissue:blood partition coefficients, the rate of metabolism of the chemical, organ volumes, organ blood flows and ventilation rates in humans. Laboratory data on two industrially important chemicals — styrene and methylene chloride — were used to illustrate the PB-PK approach. At inhaled concentrations near their respective 8-hr Threshold Limit Value — Time-weighted averages (TLV[®] — TWAs), both of these chemicals are primarily eliminated from the body by metabolism. For these two chemicals, the appropriate risk indexing parameters are integrated tissue dose or total amount of parent chemical metabolized. Since methylene chloride is metabolized to carbon monoxide, the maximum blood carboxyhemoglobin concentrations also might be useful as an index of risk for this chemical. These examples also illustrate how the model can be used to calculate risk based on various other measures of delivered dose. For the majority of volatile chemicals, the parameter most closely associated with risk is integrated tissue dose (*i.e.*, the cross product of time and blood concentration, not simply peak blood concentration). This analysis suggests that when pharmacokinetic data are not available, a simple inverse formula may be sufficient for adjustment in most instances and application of complex kinetic models unnecessary. At present, this PB-PK approach is recommended only for exposure periods of 4 to 16 hr/day. Pharmacokinetic approaches alone should not be relied on for exposure periods greater than 16 hr/day or less than 4 hr/day, because the mechanisms of toxicity for some chemicals may vary for very short- or very long-term exposures. For these altered schedules, more biological information on recovery in rest periods and changing mechanisms of toxicity are necessary before any adjustment is attempted.