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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.

Introduction

In recent years there has been increasing interest in establishing general guidelines for setting chemical exposure limits for workshifts of either shorter or longer duration than the standard 8 hr/day, 5 day/week work schedule. Various approaches have been proposed, the literature on this topic has been reviewed concisely[1] and a book chapter has been devoted to it.[2] In 1975, Brief and Scala[3] proposed a simple ratio and proportion approach for adjusting the 8-hr TLV for longer exposures to account for both the longer duration of exposure and for the reduced recovery time between exposures. These researchers acknowledged that this was a tentative proposal until sufficient work experience was accumulated that might allow for development of a more detailed model based on sound toxicological or pharmacokinetic principles.

More recently, pharmacokinetic modeling approaches have been advocated.[4-9] In these particular approaches, the peak body burden of the chemical was assumed to be the most likely parameter governing the toxicity, and circulating blood concentrations were employed as the measure of body burden. The limits for nonstandard exposure periods were derived so that the peak blood concentrations achieved during the nonstandard period would be indentical to those expected after 8 hr of exposure at the TLV concentration. Thus far, the pharmacokinetic models — except for Veng-Pedersen's — have been simple, one-compartment models and assume mono-exponential accumulation during exposure and mono-exponential elimination at the cessation of exposure. In their present form, these models require an estimate of the half-life of the particular chemical to derive an adjustment factor. Usually, in an effort to maintain simplicity, the method for determining the half-life has not been very rigorous.

The most widely accepted approaches[4-7] have recommended that a chemical's biologic half-life be determined by phenomenological observations or be estimated based on the blood:air partition coefficient of the chemical. With the so-called poorly metabolized volatile anesthetics, it is known

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TABLE I
Risk Indexes for Various Classes of Chemicals

Class of Toxicant	Appropriate Risk Index
Irritant gases	Maximum air concentration
Cholinesterase inhibitor	Blood acetylcholine esterase
Heavy metal	Total daily dose
Genotoxic carcinogen	Monthly, annual or lifetime dose
Industrial solvents	Depends on mechanism of toxicity

TABLE II
Potential Indexing Factors for Adjusting Occupational Exposure Limits for Unusual Work Schedules

Airborne concentration (exposure correlate)
Airborne concentration × time
Blood concentration (body burden)
Blood concentration × time
Metabolite concentration
Metabolite concentration × time
Target tissue concentration
Target tissue concentration × time

that half-life increases with increasing solubility. With metabolized vapors, however, these approaches can be very misleading since a single experiment determination of the half-time values does not provide meaningful information about the biochemical and physiological processes that regulate chemical disposition over a range of exposure concentrations.[10] Despite these limitations, the important conceptual advantage of these pharmacokinetic models was the idea of indexing risk at the TLV to an internal measure of dose (*i.e.*, average or peak blood concentration), and then adjusting the exposure level so that persons exposed during long shifts would have blood levels that do not exceed those obtained on normal shifts and are therefore at no greater level of risk.

The purpose of this paper is to describe a physiological model for calculating adjustment factors for unusual exposure schedules and to argue that peak blood levels and so-called peak body burden, in general, are not the most appropriate index for adjustment. At this state of its development, the proposed model is recommended only for use during workshifts similar to the standard 8-hr on, 16-hr off schedule. Specifically, this PB-PK approach should be useful for workshifts of 4- to 16-hr duration. It is not intended for application to continuous exposures or to very short-term exposure periods. Two chemicals — styrene and methylene chloride — are used to illustrate the PB-PK approach to selecting appropriate exposure limits for most nonstandard work schedules.

Methods and Model Development

Risk Indices

Central to the development of an appropriate physiological model for adjusting limits for nonconventional workshifts is the need to identify and quantify the degree of risk associated with an 8-hr exposure to a chemical at its TLV so that the calculated limit for the long schedule poses no more than an equivalent risk. For chemicals that possess a particular kind of toxic effect, it is a relatively straightforward task to adjust the exposure limit (Table I). For many irritant gases, a ceiling TLV (C-TLV) has been established to avoid air concentrations that produce direct irritant effects on the lungs or mucous membranes. In these cases, the parameter most likely to control the intensity of adverse response, which will be defined as the risk index, is the maximum concentration in air. Consequently, for irritants, the ceiling value is the TLV — irrespective of the duration of the workshift. At the other extreme are chemicals with long biological half-lives (greater than 400 hr) where the total accumulated body burden is the obvious parameter that will determine the severity of the response (*i.e.*, the risk index). With these latter materials, many of which are heavy metals or very high molecular weight lipophilics organics, there is a daily or weekly limit implicit in the TLV and that amount (dose) becomes the basis by which the daily limit can be established. In these cases, adjustments to exposure limits are based on a simple ratio and proportion approach. For example, if 1 mg/m^3 is the 8-hr TLV, then 0.67 mg/m^3 would be the 12-hr exposure limit.

At least half the chemicals for which TLVs have been established have systemic toxic effects (*i.e.*, at tissues other than at the site of entry) and possess biologic half-lives that are not dissimilar to the duration of exposure in most workplaces (*e.g.*, 6 to 12 hr). For these industrial chemicals something must be known about the mechanism of toxicity before the most appropriate risk index and adjusted occupational limits can be calculated. For irritants, as shown by the dotted line in Figure 1, the concentration that causes discomfort

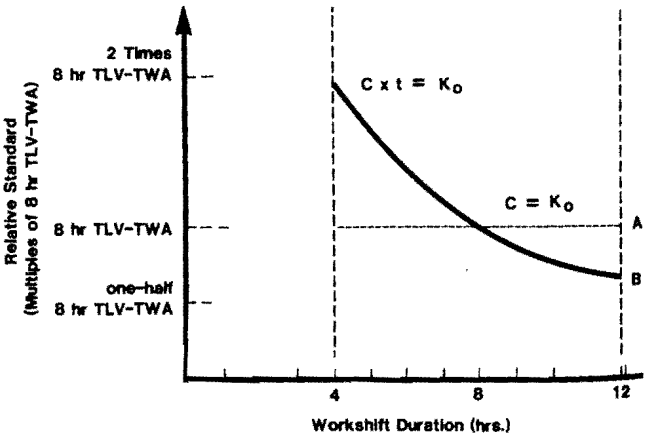
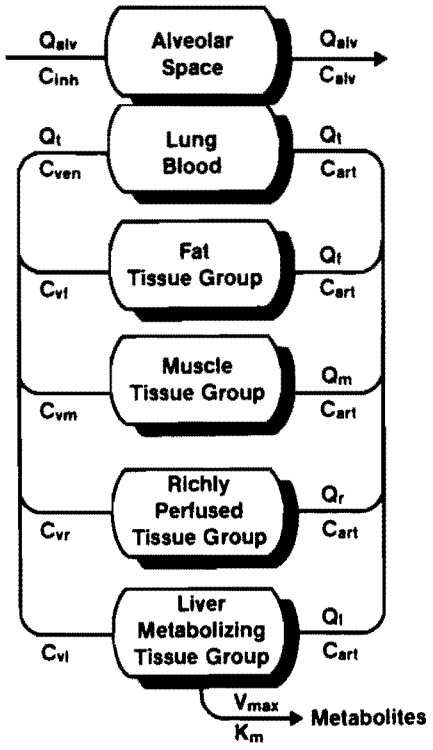


Figure 1 — Strategies for adjusting 8-hr TLV-TWA to workshifts of shorter or longer duration — For irritants where a given airborne concentration has an effect, there would be no difference in proposed TLV regardless of workshift duration (dotted line). For cumulative toxicity, the TLV is related inversely to the workshift duration (solid line). It is not immediately obvious how adjustments should be made for most industrial vapors other than they should lie somewhere between the dotted and solid lines.

will be the exposure limit regardless of exposure duration. For cumulatively acting chemicals, such as persistant PCBs or lead, shown in Figure 1 as the solid line, the relationship is a hyperbola where the TLV is related inversely to exposure duration. Most TLVs for industrial chemicals, however, will lie somewhere between the dotted and solid lines. The objective of any approach to adjusting limits, including the PB-PK approach, is to avoid excessively conservative assumptions which would recommend unnecessary expensive controls but are realistic in establishing the correct index by which the internal dose of the contaminant can be assessed (Table II).

With pharmacological agents possessing a beneficial or medicinal action, the measure of biologic activity usually is related to the peak blood concentration, in part, due to the reversible interaction of these drugs with specific receptors in the body. The toxicity of most industrial chemicals, however, is related to the average tissue concentration over a given period of time (*i.e.*, the cross product of blood concentration and time) and not simply to the peak concentration.[11] In many instances, the toxic effects of industrial chemicals are related to the metabolite of the chemical rather than the parent molecule.[12] For these, at low tissue concentrations, the rate of metabolism will be directly proportional to concentration, and usually the amount metabolized during an exposure period also will be related to the concentration and time (duration) cross-product. Consequently, based on our understanding of the toxicity of the majority of industrial chemicals, and irrespective of whether the parent chemical or a metabolite is toxic, the preferred risk index seems to be the C×T product for the target tissue. Since the kinetic data on blood concentrations often are known or easily determined and the target tissue concentrations are not known and often difficult to acquire, pharmacokinetic techniques are used to predict the contaminant concentration in the key tissues.[13-19] Such approaches usually assume that the C×T cross-product for tissues in the richly perfused tissue group (liver and kidney) are directly proportional to the C×T cross-product for the blood. In general, this seems to be a valid assumption for most gases and vapors found in the workplace.



Where:

- Q_{alv} Alveolar ventilation rate (liters air/hr)
- C_{inh} Concentration in inhaled air (mg/liter air)
- C_{alv} Concentration in alveolar air (mg/liter air)
- C_{exh} Concentration in exhaled air (mg/liter air)
- λ Blood air partition coefficient (liters air/liter blood)
- Q_t Cardiac output (liters blood/hr)
- C_{art} Concentration in arterial blood (mg/liter blood)
- C_{ven} Concentration in mixed venous blood (mg/liter blood)
- V_{max} Maximum enzymatic reaction rate (mg/hr)
- K_m Michaelis constant for enzymatic reaction (mg/liter blood)
- Q_i Blood flow rate to tissue group (liters blood/hr)
- V_i Volume of tissue group (liters i)
- C_i Concentration in tissue group (mg/liter i)
- A_i Amount in tissue group (mg)
- C_{vi} Concentration in venous blood leaving tissue group (mg/liter blood)
- P_i Tissue: blood partition coefficient (liters blood/liter i)

Where subscripts (i) for tissue groups or compartments:

- l Liver (metabolizing tissue group)
- f Fat tissue group
- m Muscle (lean) tissue group
- r Richly perfused tissue group

Figure 2 — Illustration from Ramsey and Andersen.[10] of how the body is described in physiologic pharmacokinetic modeling.

Physiological Modeling Method

A physiological approach for examining the kinetic behavior of inhaled vapors and gases which are essentially non-irritating to the respiratory tract has been developed.[10] In this description (Figure 2), the body has four lumped tissue groups corresponding to 1) highly perfused organs, excluding the liver, 2) muscle and skin, 3) fat, and 4) organs with high capacity to metabolize the inhaled chemical. The physiological parameters of the metabolizing tissue groups are essentially those for the liver.

To describe the metabolism and fate of a chemical in humans, or any living organism, basic biological and physiological data on the species must be used. The concentration of the inhaled contaminant in venous blood leaving each tissue can be determined by the tissue-blood partition coefficient. Blood flows and organ volumes were set consistent with literature values for these parameters. Organ partition coefficients and metabolic constants for each chemical are determined by simple laboratory experimentation.[10]

An essential element of the physiological models is a determination of the solubility of the test vapors in various biological fluids and tissues. For vapors, solubility is quantified by determining appropriate partition coefficients. Partition coefficients relate the relative amount of material in the liquid and gaseous phases at equilibrium. A blood:air partition coefficient of ten means that there is ten times as much substances in a unit volume of blood as in a corresponding unit volume of air at equilibrium. Partition coefficients can be determined for blood and tissues by a vial equilibration technique in which small amounts of test chemical vapors are added to the head space above the biological samples.[20]

TABLE III
Physiological Parameters for the Rat and Man Which Were Used in the Computer Simulation and Scale-up Methodology

Parameter	Rat (0.30 kg)	Man (70 kg)
Cardiac output (L blood/hr)	5.64	256
Alveolar ventilation (L air/hr)	4.5	254
Tissue volumes (% of total):		
Liver	4%	4%
Fat	9%	20%
Muscle	75%	62%
Richly perfused organs	5%	5%
Blood flow (% of total):		
Liver	25%	25%
Fat	9%	9%
Muscle	12%	12%
Richly perfused organs	54%	54%

After equilibration, the head space is sampled for test chemical. The partition coefficient is determined by a calculation based on the difference between the amount in the test vial and that in a control vial. Tissue:blood partition coefficients are determined by dividing the tissue:air by the blood:air values.

These various constants are used in the four mass balance differential equations that describe the time-dependent changes of tissue concentration in each of the compartments. Mixed venous blood concentration is determined as the weighted sum of effluent blood concentration from each tissue group, and the arterial concentration is determined from inhaled air concentration and venous blood concentration on the assumption that arterial blood leaving the lung is equilibrated with end alveolar air. Specifically, cardiac output was assigned a value of 5.64 L blood/hr for a 0.30 kg rat, and to maintain a ventilation:perfusion ratio of 0.8, alveolar ventilation was set equal to 4.50 L air/hr. The liver, fat, muscle and richly perfused tissue groups in the rat were assigned volumes respectively equal to 4%, 7%, 75% and 5% of body weight. Blood flow distribution to the liver, fat, muscle and richly perfused tissue groups was respectively, 25%, 9%, 12% and 54% of cardiac output (Table III).

Once the model and constants are developed, simultations of expected behavior were conducted with a commercial software package (Advanced Continuous Simulation Package, Mitchell and Gauthier, Cambridge, Mass.) on a CDC 7600 Computer. This approach has been used extensively to study the kinetics of inhaled styrene in both rats and human volunteers.[10,13] These physiological models can be used to extrapolate from high concentrations to predict behavior at low inhaled concentration and to extrapolate from results in rats to predict expected behavior in humans. This approach to interspecies extrapolation based on physiological models has been called animal scale-up.[14-15] Simulated human curves in this paper are calculated by scale-up of the model used to describe styrene kinetics in rats.[10]

Results

Application of the PB-PK Model to Styrene

Styrene is a reactive monomer and is readily soluble in blood and, especially, in fat, as is evident from its partition coefficients in these tissues (Table IV). The kinetic constants for the oxidative metabolism of styrene in 300 g rats (Table V) were determined from steady-state inhalation exposures.[13] These constants were used to simulate kinetic behavior in rats with the use of a physiologically-based inhalation model that has been developed over the past four years.[10,16-18] The resulting computer simulations were compared to actual laboratory data obtained from rats exposed to styrene for 6 hr and then rested for an 18-hr period immediately after exposure.[19] Physiological parameters for rats used in the simulation were obtained from the literature and are summarized in Table III.

The computer model successfully predicted the actual kinetic behavior in rats at four different exposure concentrations. It also reproduced the complex change in kinetic behavior observed in proceeding from low vapor concentrations where metabolism is linear to high concentrations where metabolism is saturated (Figures 3a and 3b). The scale-up to man (Figures 3c and 3d) gave a good description of data already available in the literature. These data were obtained from human volunteers exposed to 80 ppm for 6 hr (Figure 3c). These plots show both venous blood and end alveolar air concentrations.[19] Another set of literature data[21] also was simulated successfully with the model (Figure 3d). The smooth curves are from the computer simulations, and the various symbols represent the actual data.

TABLE IV
Partition Coefficients

	Tissue Reference	Styrene	Methylene Chloride
Rat:	blood:air	40.2 ± 3.7	19.4 ± 0.8
	fat:air	3476.0 ± 73.0	120.0 ± 6.0
	liver:air	139.0 ± 7.0	14.2 ± 1.2
	muscle:air	47.0 ± 4.0	7.9 ± 1.8
	olive oil:air	3548.0 ± 269.0	131.0 ± 7.0
Human:	blood:air	51.9 ± 2.0	9.7 ± 0.4

TABLE V
Metabolic Constants in Rats

	Constant	Styrene	Methylene Chloride
Rats:	Maximum velocity	3.6 mg/hr	1.7 mg/hr
	Binding constant	0.4 mg/L	0.4 mg/L
Humans:	Maximum velocity	165.0 mg/hr	78.0 mg/hr
	Binding constant	0.4 mg/L	0.4 mg/L

$$\text{Rate of metabolism} = \frac{V_{max}\,[\text{styrene}]}{K_m + [\text{styrene}]}$$

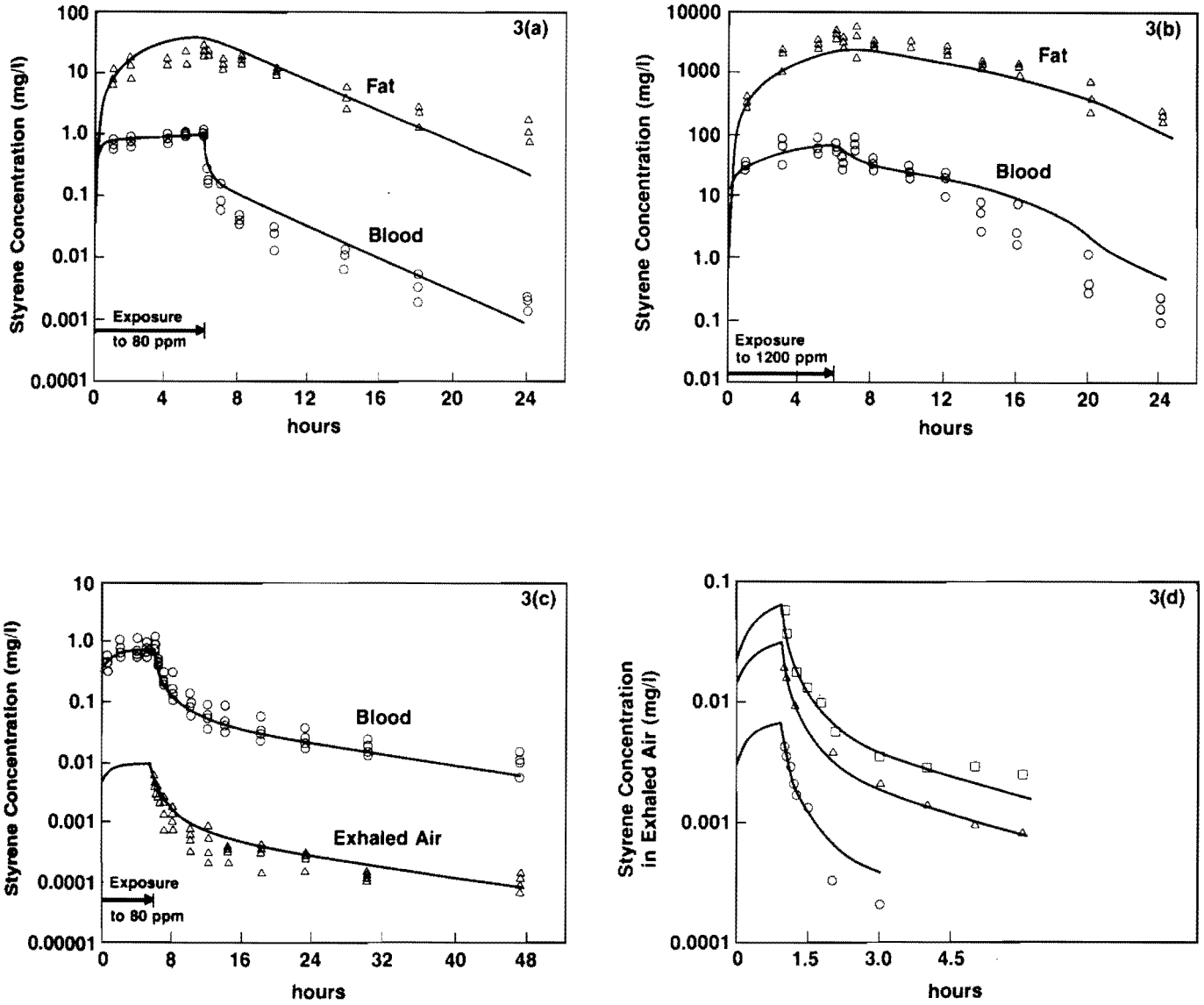


Figure 3 — Physiological modeling results for inhaled styrene in rats and humans — A physiological model was developed to analyze blood and fat time course curves during and after inhalation of styrene by rats. Panels A and B show data points and model predictions for low (80 ppm) and high concentration (1200 ppm) behavior. Data are from Ramsey and Young.[19] Note the marked difference in behavior at the high inhaled concentrations where metabolism is saturated. Panels C and D are comparisons of data from human volunteers and model predictions. The model was not adjusted to give a good fit to the curves; the rat model was scaled-up and used to predict human behavior. Data in Panel C are from Ramsey and Young[19] for humans exposed for 6 hr. Data in Panel D are from Stewart *et al.*[21] for the post-exposure exhaled air concentration following a 1-hr exposure.

As is apparent, the PB-PK requires some knowledge of the chemical's mechanism of toxicity and certain information on the partition coefficient and metabolic constants in humans. Partitioning and metabolism data will be most often available for rat tissue, and the values in humans frequently can be determined by extrapolation of the rat data or by limited *in vitro* or *in vivo* experimentation in humans. For example, human blood partition coefficients can be determined readily with the vial equilibration approach, and for many volatile organics, the V_{max} can be approximated as a partial power of body weight.

The current TLV-TWA for styrene is 50 ppm.[22] As yet, there is no definitive understanding of the mechanism of its toxicity. Consequently, it is uncertain whether one should establish an exposure limit that will prevent attaining a specific circulating blood concentration or a concentration-time cross-product. One reason for the uncertainty is that styrene might have the potential of being mutagenic since it is metabolized *via* an epoxide intermediate that is hydrated subsequently to phenyl ethylene glycol. If the electrophilic epoxide metabolite eventually is found to be responsible for styrene's toxicity, the blood concentration-time cross-product would be the best risk index for establishing modified exposure limits.

A significant advantage of the physiological models is their capacity to keep track of the areas under the blood or tissue curve or the area under the rate of metabolism curve. In this case, risk indexing is done by first determining the

8-hr area-under-the-blood-curve (sometimes called AUC in pharmacokinetic literature) for exposure at a particular concentration (Figure 4a), which in this example was 100 ppm (*i.e.*, twice the present TLV). Subsequently, the model can be run for any other exposure times, *e.g.*, 10 or 12 hr, and for a variety of concentrations. From these data, vapor concentrations for these longer exposures that pose the same level of risk can be determined (Figure 4b).

By using this approach and assuming that the area under the blood/concentration is the best way to assess the risk associated with styrene exposure, it was determined that a 12-hr exposure to 64 ppm was equivalent to an 8-hr exposure at 100 ppm. Conversely, if achieved blood concentration had been chosen as the appropriate risk index (Figure 4c), the proposed 12-hr limit would have been only 97 ppm (Figure 4d). Clearly, the choice of index has a major influence on the magnitude of the adjustment required to equate the 12-hr risk index with that observed in the 8-hr exposure.

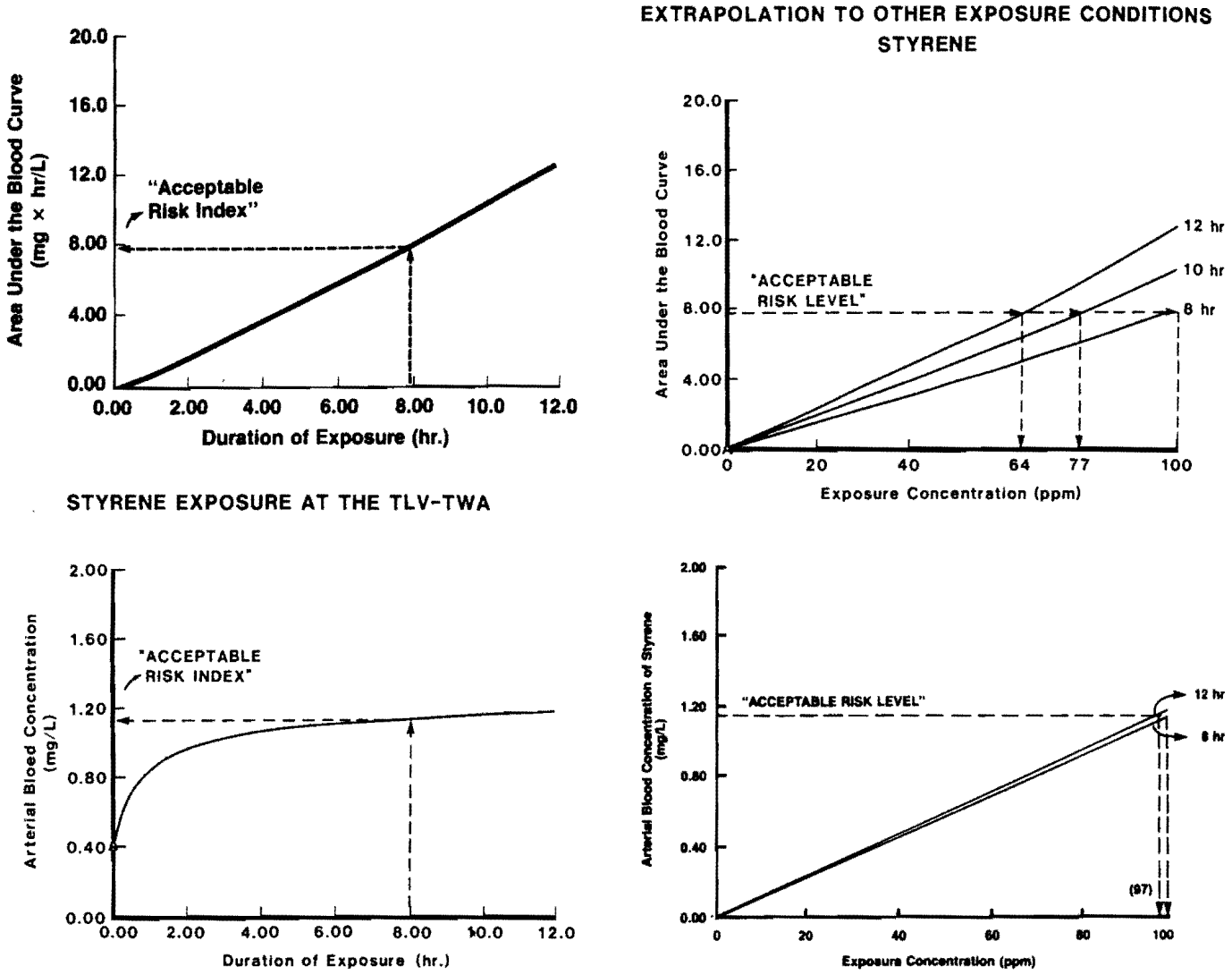


Figure 4 — Shift adjustments using a physiological pharmacokinetic approach — Panel A: After the decision is made about the appropriate measure of tissue dose, the human PB-PK model is exercised at the TLV-TWA and the acceptable risk index determined for the 8-hr exposure. In this case, you find 8 hr on the X-axis and read off the accumulated area under the blood curve. Panel B: The curve in Panel A is obtained by running a kinetic model at a single concentration. The curves in Panel B are different. In this case the models are run for many concentrations with a specified exposure duration. The output of these so-called repetitive runs are used to contruct a composite curve relating target tissue dose to various exposure concentrations. Three curves were generated for exposure durations of 8, 10 and 12 hr. In order to calculate the adjusted TLV, the risk index from Panel A is used on the Y-axis and a line drawn parallel to the X-axis. The shift adjusted TLV-TWA then is determined from the intersection with the particular workshift curves. Panel C: Shift adjustments based on peak blood concentrations —The PB-PK model is run to estimate the time course of styrene in blood and the value for the 8-hr exposure (*i.e.*, the acceptable risk level) is read off the curve. Panel D: Adjusting the TLV to a nonstandard, a 12-hr shift — The model is exercised for exposures of 8 or 12 hr for a variety of exposure concentrations and end exposure peak blood styrene concentration plotted *vs.* exposure concentration. The new 12-hr TLV-TWA is determined as in Panel B by taking the risk level from the Y-axis and drawing the line parallel to the X-axis to its intersection with the 12-hr curve. This is the new acceptable exposure level.

Application of the PB-PK Model to Methylene Chloride

In rats, methylene chloride (CH_2Cl_2) is metabolized to carbon monoxide (CO), which binds with hemoglobin to form carboxyhemoglobin (HbCO). Exposure standards for both CO itself and CH_2Cl_2 are aimed at keeping circulating HbCO concentrations at no more than 5% of the total hemoglobin. This is a case where the risk index clearly is identified and it is not simply the C×T cross-product of the parent molecule, CH_2Cl_2. Consequently, the TLV for methylene chloride for the non-standard workshift will be designed to keep end-of-shift HbCO concentrations at levels no greater than those observed after 8-hr exposure at the current 8-hr TLV-TWA of 100 ppm. A physiological pharmacokinetic model that simulates both the CH_2Cl_2 blood concentrations and the increased HbCO concentrations associated with CH_2Cl_2 metabolism to CO was developed recently.[18,23] The model keeps track of the amount of parent CH_2Cl_2, the amount converted to CO and the circulating HbCO concentration. This model describes the increased blood carboxyhemoglobin concentrations that result from inhalation of carbon monoxide (Figure 5a) as well as the HbCO levels caused by inspiration of CH_2Cl_2 (Figure 5b). Blood levels of CH_2Cl_2 also are predicted accurately by this PB-PK approach. As before, smooth curves illustrate the computer simulations based on the physiological model with the use of the measured partition coefficients and metabolic constants for CH_2Cl_2 in rats (Table IV and V). This model, like that for styrene, also can be scaled readily to predict the kinetic behavior of CH_2Cl_2 in humans. Both the cumulative area under the blood curve and the percentage of carboxyhemoglobin can be determined for various times of exposure at 100 ppm CH_2Cl_2 (Figure 6). Interestingly, blood carboxyhemoglobin approaches a steady-state level, whereas area under the curve increases nearly linearly with duration of exposure. The blood carboxyhemoglobin concentration at 8-hr exposure to 100 ppm is expected to be about 6%. This includes a background contribution for CO that is simulated in the model as an ambient inhaled CO concentration of 2.2 ppm, and a certain rate of endogenous CO production related to heme catabolism.

As with styrene, the methylene chloride data on rats were scaled-up with the use of the human model for given exposures of 8, 10, or 12 hr at various vapor concentrations. In this case, end-exposure carboxyhemoglobin concentrations were calculated and plotted as a separate curve for each exposure duration (Figure 7a). The nonstandard workshift TLV then can be read-off the plot by drawing a line from the 8-hr curve at 100 ppm to the Y-axis (*i.e.*, at the acceptable risk level). For controlling carboxyhemoglobin, a recommended 12-hr occupational exposure limit would be 78 ppm and a recommended 10-hr TLV-TWA would be 85 ppm (Figure 7a). Recently, there has been concern expressed that reactive products formed in CH_2Cl_2 metabolism may have carcinogenic or mutagenic potential.[24] If this were true, the risk index would be related to the area under the blood curve. The 12-hr TWA-TLV calculated on that basis would be reduced to about 63 ppm (Figure 7b).

Conclusions

Establishing scientifically sound chemical exposure limits for nonstandard or unusual workshifts is a difficult but pressing industrial hygiene problem. Standards for unusual workshifts should not be unnecessarily conservative since

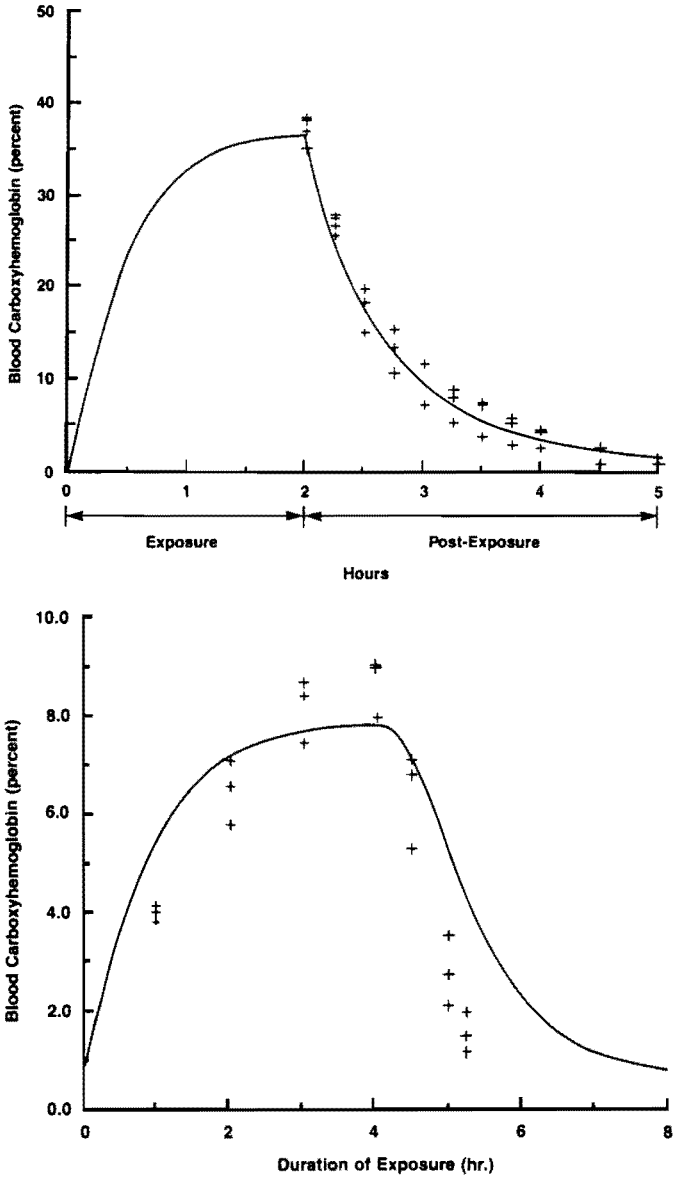


Figure 5 — Increased blood carboxyhemoglobin (HbCO) levels associated with inhalation of carbon monoxide or methylene chloride (CH_2Cl_2) by rats. Recently, Gargas *et al.*[23] described a PB-PK model for CH_2Cl_2 inhalation and included both CO and HbCO concentrations in their description. Panel A: Loss of blood HbCO in three individual rats following a 2-hr exposure to 500 ppm CO. The smooth curve is from the CH_2Cl_2 PB-PK model in which inhaled CH_2Cl_2 concentration is zero. Panel B: Blood HbCO during and after a 4-hr exposure to 198 ppm CH_2Cl_2 and 0 ppm CO. Smooth curve is a prediction from the PB-PK model of Gargas *et al.*[23] The model is based on a prediction of blood HbCO levels developed by Coburn, Forster and Kane[25] and the physiological parameters on which it is based are readily scaled with body weight to predict human behavior.

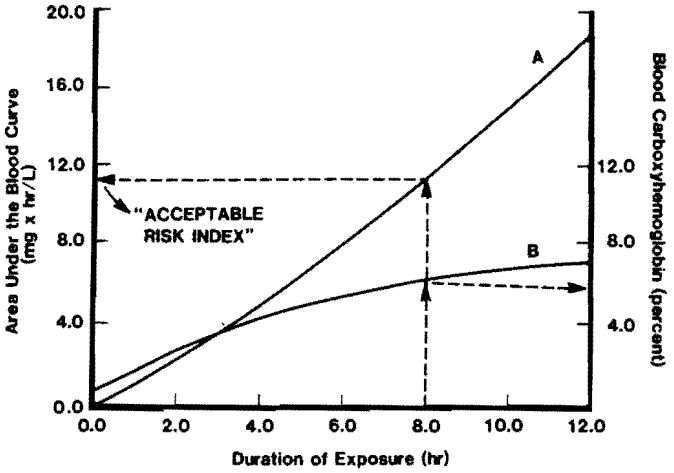


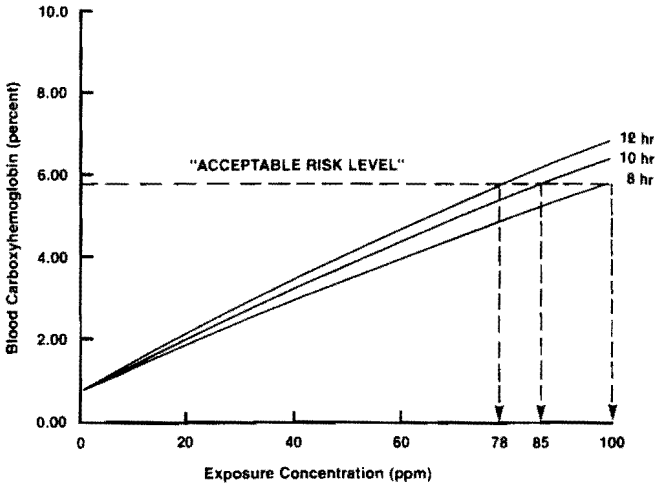
Figure 6 — Determining appropriate risk indices for methylene chloride inhalation for 8-hr exposures at 100 ppm, the TLV-TWA. For CH_2Cl_2, two risk indices were examined by the physiological model — AUBC and blood HbCO. A simulation was run for a 12-hr exposure and, among other parameters, AUBC and HbCO were calculated at various times of exposure to create the two curves. The 8-hr TLV-TWA risk index is estimated by the value of the parameters at the 8-hr time point.

they could place severe engineering constraints on important industrial processes that might divert funds away from more important occupational health hazards. Yet, they must be as accurate as possible, and to do this, they should equate a particular chemical exposure with the proper measure of dose at the target tissues. The approach outlined in this paper meets these objectives since it recommends adjustment factors for unusual periods of exposure that are based on sound pharmacokinetic and toxicological principles.

To use this approach, some information is needed on the mechanism of toxicity, tissue partition coefficients, and metabolic coefficients for each chemical. With this data in hand, a rigorous predictive pharmacokinetic approach can be used to estimate the nonstandard workshift exposure level based on a risk index used in the original 8-hr TWA-TLV. Because of the considerable amount of biologic and physical chemical data required, the approach will have to be applied on a compound by compound basis. This is, however, not unlike the pharmacokinetic approaches that previously have been proposed in which the biological half-life must be determined.[4-7]

The mathematics employed in the physiological-pharmacokinetic approach are based on simulation techniques associated with the numerical integration of systems of differential equations. Software for solving these systems of equation is widely available and now can be implemented on microcomputers. Laboratory data — such as partition coefficients and metabolic constants — are also relatively easy to determine with the use of recently described approaches.[13,20,23] These data are currently in the literature for as many as 40 common industrial chemicals.

Previous approaches using pharmacokinetic analysis assumed simpler disposition of the chemicals in the body and gave mathematical equations with exact solutions. The present method simply develops the particular equations, and the computer calculates predicted kinetic behavior. In the final analysis, it is not the form of the mathematics that is important. The mathematical solutions of the differential equations are straightforward and are not a serious limitation to its widespread use. The primary difficulty in use of this model is the lack of detailed knowledge regarding the mechanisms of toxicity of many chemicals. The authors believe such information is needed to select accurately the appropriate risk index to be used in the calculations. Just as



EXTRAPOLATION TO OTHER EXPOSURE CONDITIONS METHYLENE CHLORIDE

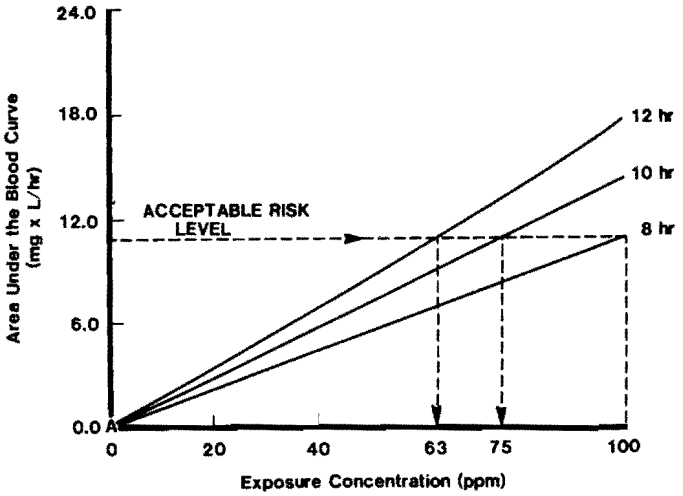


Figure 7 — Adjusting the TLV-TWA for CH_2Cl_2 based on a physiologically based pharmacokinetic model. Panel A: The CH_2Cl_2 model for humans is exercised at a variety of concentrations (each solid curve) for varying exposure durations. The adjusted TLV determined by the exposure concentration is the 10- or 12-hr exposure that produces the same HbCO level as predicted by the 8-hr exposure to 100 ppm. The 10- and 12-hr TLVs are estimated as 85 and 75 ppm, respectively, based on blood HbCO. Panel B: When area under the blood CH_2Cl_2 curve is used, the 10- and 12-hr TLVs now are reduced to 75 and 63 ppm, respectively, when the PB-PK model is used for adjustment.

in deriving an initial value for a TLV, sound toxicological and epidemiological evidence from human exposure experience is required to derive the proper risk index for whatever modeling is attempted. Good judgment is the most important part of this risk analysis procedure. The mathematical modeling is very simple and not at all the limiting step in this procedure.

For most industrially important gases and volatile liquids, toxicity will more likely be related to the area under the blood curve than to peak blood concentration. For the sake of simplicity, a simple inverse relationship (Figure 1, Line B) might be an acceptable way of adjusting many TLVs, since the risk index calculated when an area under a concentration curve is used will be nearly identical to that derived from the inverse relationship. For adjustments with shifts of 4 to 16 hr/day, an application of this PB-PK approach is recommended whenever possible, or reliance on the direct ratio/proportion approach (Figure 1, Line B) if there is an insufficient amount of biologic data to formulate a PB-PK model. For exposures of less than 4 hr or greater than 16 hr, PB-PK modeling is presently inadequate since information would be necessary on recovery in rest periods and changing toxic mechanisms in very acute or more chronic exposures before adjustment should be attempted.

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