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A one-compartment exponential model is described which predicts "equal protection", based on biological uptake rates, for unusual air contaminant exposure situations as compared to a "normal" exposure of five 8-hour days per week. This is done by equating peak body burdens resulting from a normal and an unusual exposure, in terms of an adjustment factor applied to the normal exposure limit for an air contaminant. This factor predicts the highest allowable concentration in an unusual exposure situation which will not result in a higher-than normal body accumulation of the inhaled substance. Graphs and formulae are provided for determining adjustment factors for anticipated unusual exposure schedules. The model's predictions and published data are compared.

Application of occupational exposure limits to unusual work schedules

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introduction

Regulatory standards for occupational exposure to chemical air contaminants,[1] administered by the Occupational Safety and Health Administration (OSHA), are largely derived from threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists.[2] Both the TLVs and the OSHA permissible exposure limits (PELs) are based on exposure during a normal workweek of five 8-hour days. There is thus a need for some method to apply OSHA exposure limits to unusual work schedules. Parts of this need have been addressed by short term exposure limits[2,3] and by limits applicable to both 8 and 10-hour workdays[4,5] or to longer than normal shifts.[6,7] Although many of these systems have not taken biological uptake and excretion directly into account, two models for applying exposure limits to unusual exposure situations do consider the importance of biological uptake and excretion.[8,9] The model described herein is an extension of these two systems and is based on the following two principles. First, the intensity of toxic action is a function of the concentration of a toxic substance that reaches the site action,[10] and second, exposure to a substance in air at its TLV (or PEL) for five 8-hour days per week (which will be called "normal exposure") results in some burden in the body which by experimental observation or experience has been inferred to be an acceptable exposure for most workers.[2]

It is therefore the purpose of this model to derive a means for determining a special exposure limit which will predict equal protection to the worker in a special exposure situation that the TLVs (or PELs) provide in a "normal" exposure situation. This special limit would be expressed as a decimal adjustment factor which, when multiplied by the prescribed limit, would yield the special limit. This approach does not assert that currently prescribed or recommended limits are safe, but only that the special limit should predict "equal protection" during a special exposure situation.

Several indices of body or tissue burden are candidates for predicting equal protection in two different exposure situations. These are peak, average, and residual body burden of a substance. Peak body burden was selected for use in this model, as being most reflective of peak toxic effect of a substance at the site of action.[10] Limitations of the other two indices are discussed in a later section.

the one-compartment model

When a substance (particulate, gaseous, or vapor) is inhaled in air, it is taken up by the body, distributed, perhaps metabolized, and excreted by complex processes. Several mathematical models are available for describing these processes.[9,11-16] The one-compartment model was chosen for this project. It is the simplest uptake-excretion model, and assumes that the body is an homogenous mass, comparable to a room or compartment containing a clean fluid, such as air. More of the air, bearing a contaminant, enters and flows continuously through the compartment, mixing en route with the air therein, in a process analogous to inhalation. If contaminated air continues to enter, the contaminant concentration in the compartment increases until it reaches equilibrium with that of the incoming air; that is, as much contaminant is leaving as entering. When the contaminated air supply is replaced with clean air, the process is reversed, and the contaminant concentration in the compartment decreases exponentially. This action is described by the following equations.

For uptake: $B_t = CWK\,(1 - e^{-kt}) + B_o(e^{-kt})$ **(1)**

For excretion: $B_r = B_t\,(e^{-kt_r})$ **(2)**

in which:

- B_t = body burden of substance at time t (mass);
- B_o = initial body burden of substance at time zero (mass);
- B_r = residual body burden of substance at time t_r (mass);
- C = substance concentration in air (mass/volume);
- K = ratio of the substance's equilibrium solubility in the body to that in air, or "partition coefficient" (dimensionless);
- W = volume of body (volume);
- k = uptake and excretion rate of substance in the body, equal to L/WK, in which L is the flow rate of air to the body ($time^{-1}$);
- t = time of exposure to substance in air (time);
- t_r = time since cessation of exposure to substance in air (time).

It should be noted that k may also be expressed in terms of half-life or half-time of the substance in the body, $T_{1/2}$, where $k = (\ln 2)/T_{1/2}$.

Figure 1 shows the body's uptake and excretion of an air contaminant according to equations 1 and 2, upon exposure to contaminated air during working hours and to clean air during non-working hours. During periods of exposure, the body takes up the contaminant according to rate k, and during non-working hours the body excretes the contaminant according to negative rate-k. For a given exposure schedule, the body eventually reaches some equilibrium level with the contaminated air after repeated exposures.

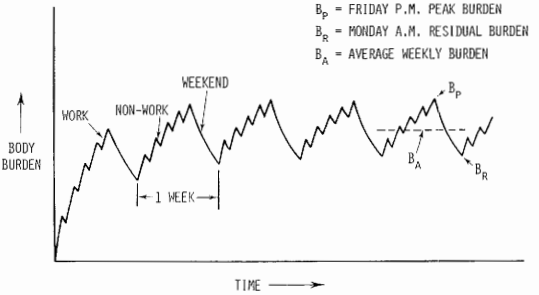


Figure 1 — Weekly fluctuation of body burden from occupational exposure to a substance in air. (Source: Ref. 16).

Figure 1 shows the variation in body burden upon exposure to an air contaminant for five workdays per week for a period long enough to reach equilibrium. Equilibrium implies that the "Monday morning"[12] body burden (B_r) remains the same from week to week for a given exposure schedule. Each schedule also has a characteristic Friday afternoon peak body burden (B_p), and average body burden (B_a).

the adjustment factor

Figure 2 depicts body burden curves for a "normal" and a non-normal exposure schedule, each having its characteristic peak, residual, and average body burdens. Since peak body burden

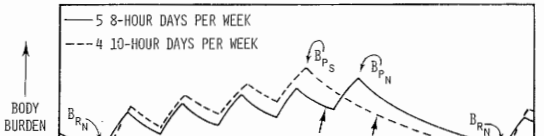


Figure 2 — Criteria for comparing effects of two exposure schedules.

(B_p) was chosen as the criterion to predict equal protection, the model must yield a special exposure limit such that the peak body burden from the special exposure (B_{ps}) does not exceed the peak body burden from the normal exposure (B_{pn}). The equations for peak body burden for a normal and for any special exposure schedule are:

For a normal schedule: $B_{pn} = C_{nwk}\,[f(k,t_n)]$ **(3)**

For a special schedule: $B_{ps} = C_s WK\,[f(k,t_s)]$ **(4)**

in which:

B_{pn} = peak body burden for a normal exposure schedule;

B_{ps} = peak body burden for a special exposure schedule;

C_n = air concentration of contaminant in normal schedule (OSHA) limit);

C_s = air concentration of contaminant in special schedule;

$f(k,t)$ = an expression indicating a first-order exponential function of k and t_n for a normal schedule and of k and t_s for a special schedule; this is expanded later.

Designation of B_p as criterion for equal protection simply means that B_{ps} is set equal to B_{pn}. Equations 3 and 4 thus devolve to:

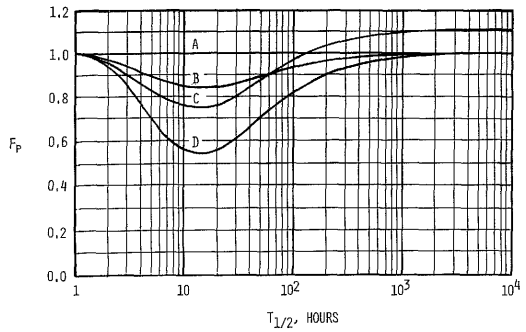
$$\frac{C_s}{C_n} = \frac{f(k,t_n)}{f(k,t_s)} = F_p \qquad \textbf{(5)}$$

The symbol F_p is now established as the ratio of the special exposure limit to the normal exposure limit. F_p is an adjustment factor which, when multiplied by the normal exposure limit (OSHA limit), yields the special exposure limit. The subscript p indicates that the adjustment factor is based on peak body burden as criterion of equal protection.

The expressions $f(k,t_n)$ and $f(k,t_s)$ may now be expanded as follows:

See equation (6) below . . .

in which t values represent duration of sequential work and rest periods in cycle T for normal (n) and special (s) exposure schedules. In this model, the use of ratios causes many of the imponderable and unknown terms to cancel, leaving only the special work schedule, which will be known, and the substance half-life (or uptake/excretion rate), which may or may not be known.



A = 5 8-HR DAYS/WK. B = 4 10-HR DAYS/WK. C = 3 12-HR DAYS/WK. D = 1 40-HR SHIFT/WK.

Figure 3 — Adjustment factor (F_p) as a function of substance half-life ($T_{1/2}$) for various exposure schedules.

application of the model

F_p may be plotted as a function of substance half-life, $T_{1/2}$, for any two schedules. This has been done in Figure 3 for a normal workweek vs. a workweek of four 10-hour days, a workweek of three 12-hour days, and a single 40-hour shift per week.

Figure 3 shows that for substances with very short half-lives, less than one hour, the peak body burden is reached very quickly and is the same for a normal workweek as for any special schedule with longer shifts. Therefore, if B_p is chosen as the predictor of equal protection, no reduction in OSHA limits is necessary for longer-than-normal work shifts.

For substances with very long half-lives in the body, the adjustment factor is proportional merely to the number of hours exposed, not the daily or weekly exposure schedule. Thus, all 40-hour weeks have a special exposure limit for such substances equal to the normal limit, or an F_p of unity. Since three 12-hour days total only

$$F_p = \frac{(1 - e^{-kT_s})\,[1 - \exp(-kt_n) + \exp(-k\sum_{i=n-1}^{n} t_i) - \ldots + \ldots - \exp(-k\sum_{i=1}^{n} t_i)]_n}{(1 - e^{-kT_n})\,[1 - \exp(-kt_s) + \exp(-k\sum_{j=s-1}^{s} t_j) - \ldots + \ldots - \exp(-k\sum_{j=1}^{s} t_j)]_s} \qquad \textbf{(6)}$$

36 hours per week, F_p for that schedule is 40/36, or 1.1, for a substance with a very long half-life.

For a substance with an intermediate half-life, F_p varies as a function of the half-life, with a worst-case condition of 0.84 for four 10-hour days, 0.75 for three 12-hour days, and 0.54 for the single 40-hour shift. Where the half-life is not known, the worst-case F_p may be used.

If the OSHA cumulative exposure formula for time-weighted-average exposures,[1] as it is now used, were applied to the 10- or 12-hour shift schedule, no reduction in exposure limits would be required, as only eight hours of the shift would be considered. This comparison illustrates how use of a biological uptake model, as contrasted to the use of air concentrations, as an index of protection could avoid higher-than-normal exposures in such situations. By contrast, if the OSHA formula[1] were extended to take into account the longer shift, as recommended by NIOSH,[6] the TWA limit would be reduced to 0.66 of the normal limit, irrespective of the substance half-life. This comparison illustrates how use of the model could avoid unnecessarily large exposure limit reductions.

Equation 6 may be used to determine an F_p for any exposure schedule. However, for regular repetitive schedules, equation 6 simplifies to:[11]

See equation (7) below . . .

in which, using hours as the time unit,

t_{1n} = length of normal daily work shift (8 hours);

t_{2n} = length of normal daily non-exposure periods (16 hours);

$t_{1n} + t_{2n}$ = length of normal day (24 hours);

T_n = length of normal week (168 hours);

n = number of workdays per normal week (5)

t_{1s} = length of special "daily" work shift, hours;

t_{2s} = length of special non-exposure periods between shifts, hours;

$t_{1s} + t_{2s}$ = length of basic work cycle, analogous to the "day", hours;

T_s = length of periodic work cycle, analogous to the "week", hours;

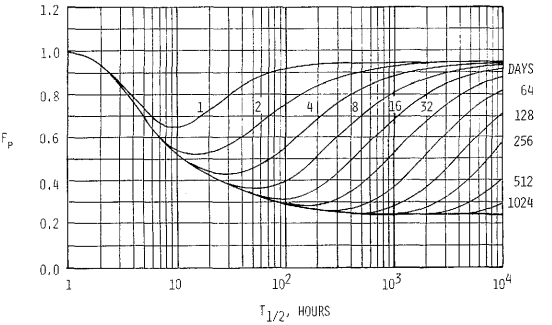


Figure 4 — Adjustment factor (F_p) as a function of substance half-life ($T_{1/2}$) for continuous exposure schedules.

m = number of work "days" per work "week" in the special schedule.

Where the special work cycle uses normal days and weeks, equation 7 simplifies further. Comparing again the five 8-hour day workweek to the four 10-hour day workweek, equation 7 reduces to

$$F_p = \frac{(1 - e^{-8k})\ (1 - e^{-120k})}{(1 - e^{-10k})\ (1 - e^{-96k})} \qquad (8)$$

Other curves may be generated from equations 6 or 7 to compare any two schedules. In Figure 4, the normal workweek is compared to continuous exposures for several periods of time from one to 1,024 days, followed by rest periods equal to three times the exposure periods. Again, for substances with very short half-lives, no adjustment to exposure limits is necessary when B_p is the criterion. For substances with very long half-lives, F_p approaches proportionality with number of hours exposed. In Figure 4, F_p approaches the ratio of 40/42, or 0.95, because the continuous exposure schedule averages 42 hours per week.

In Figure 5, the normal workweek is compared to workweeks of from one to seven 8-hour days. It can be seen that exposure limits may not be increased, even if exposure is for only one day per week, unless the substance half-life is greater than six hours. Similarly, limits need not be decreased for six or seven-day workweeks unless the substance half-life is greater than about 16 hours. For substances with very long half-lives, F_p is again proportional to hours

$$F_p = \frac{[1 - e^{-kt_{1n}}]\ [1 - e^{-k(t_{1n}+t_{2n})n}]\ [1 - e^{-kT_s}]\ [1 - e^{-k(t_{1s}+t_{2s})}]}{[1 - e^{-kt_{1s}}]\ [1 - e^{-k(t_{1s}+t_{2s})m}]\ [1 - e^{-kT_n}]\ [1 - e^{-k(t_{1n}+t_{2n})}]} \qquad (7)$$

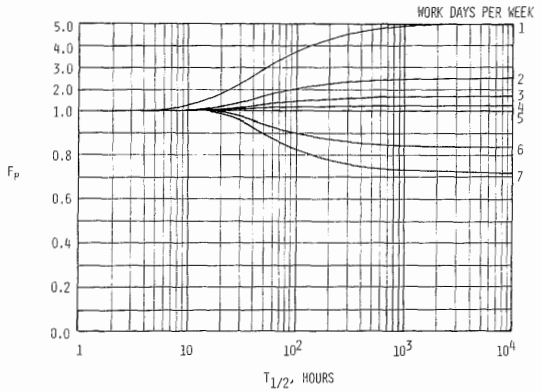


Figure 5 — Adjustment factor (F_p) as a function of substance half-life ($T_{1/2}$) for various work weeks.

worked per week, as compared to 40 hours.

The model may be used to predict the permissible level and duration of exposure necessary to avoid exceeding the normal peak burden during short, high-level exposures. The model does this by establishing excursion limits which will predict equal protection for these situations. Assuming exposure is limited to a single daily excursion of duration t_e, equation 6 reduces to

$$F_p = \frac{1 - e^{-k(8)}}{1 - e^{-kt_e}} \qquad \textbf{(9)}$$

Adjustment factors derived from equation 9 have been plotted in Figure 6 as a function of substance half-life and excursion time. To illustrate, if a worker is exposed for one 30-minute period during an 8-hour shift to a substance with a half-life in the body of 4 hours (k = 0.17), the adjustment factor would be determined as follows:

$$F_p = \frac{1 - e^{-(0.17)8}}{1 - e^{-(0.17)1/2}} = 9.0$$

The model would thus predict a limit of nine times the OSHA TWA limit.

This value may be read from Figure 6. If the OSHA cumulative exposure[1] formula were used to determine a limit, the limit would be 16 times the OSHA TWA limit, assuming no ceiling or peak limits for the substance. In Figure 6, the 15-minute curve is dotted because the one-compartment model is not precise for very short exposure times.

"supersafe" adjustment factor

In the derivation of exposure limits for

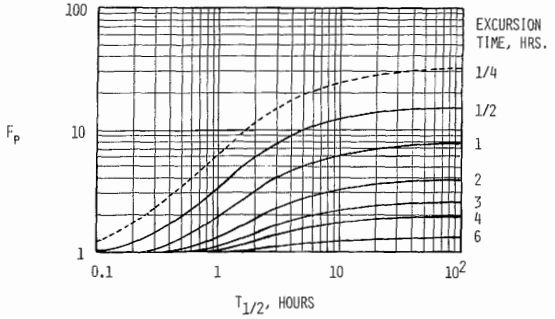


Figure 6 — Adjustment factor (F_p) as a function of substance half-life ($T_{1/2}$) and excursion time.

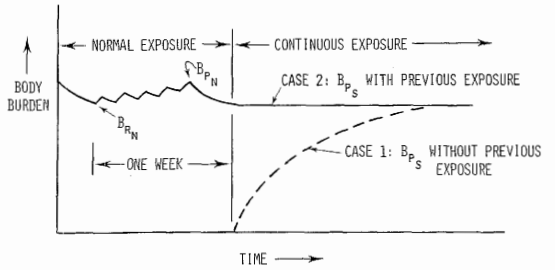


Figure 7 — Equating peak body burden for continuous exposure to residual body burden for normal exposure.

prolonged continuous exposure, such as in submarines or manned spacecraft, it may be desirable to be "supersafe" and establish as the criterion that the peak body burden for the special exposure (B_{ps}) be no greater than the residual body burden for a normal exposure (B_{rn}). This situation is illustrated in Figure 7 for two cases. In the first case, it is desired to determine an adjustment factor for exposure limits such that a person exposed continuously (but with no previous exposure) will accumulate a B_p no greater than the residual burden, B_r, acquired during normal exposure. The equation for the adjustment factor, designated as $F_{p/r1}$, is:

$$F_{p/r1} = \frac{(1 - e^{-8k})\,(1 - e^{-120k})\,(e^{-64k})}{(1 - e^{-168k})\,(1 - e^{-24k})\,(1 - e^{-kt})} \qquad \textbf{(10)}$$

in which t is the length of continuous exposure in hours.

In the second case, it is desired to determine how much to reduce the exposure concentration so that a person converting from normal to continuous exposure will not accumulate a peak body burden greater than his former residual body burden. The equation for this adjustment factor, designated as $F_{p/r2}$, is:

$$F_{p/r2} = \frac{(1 - e^{-8k})\,(1 - e^{-120k})\,(e^{-64k})}{(1 - e^{-168k})\,(1 - e^{-24k})} \qquad (11)$$

Note that the variable t has dropped out of equation 11, as the body begins its continuous exposure already at equilibrium. Equation 10, on the other hand, includes a function of t to account for the buildup time required to reach a B_{ps} equal to the former B_{rn}. Otherwise, the two equations are identical.

$F_{p/r1}$ and $F_{p/r2}$ have been plotted against substance half-life in Figure 8. The base curve (A) follows equation 11, in which previous normal exposure is assumed. The other curves follow equation 10, which assumes no previous exposure. Thus, a worker with no previous exposure may be exposed for limited periods to much higher contaminant levels, without exceeding the normal residual burden, than a worker who switches directly from normal to continuous exposure.

Figure 8 is used as follows. For a substance with a half-life of 35 hours, the special exposure limit for continuous exposure after converting from normal exposure would be 0.1 the normal exposure limit. This value is read from base curve A. However, if a worker had not been previously exposed to the substance, or degassified completely since his last exposure, he could be exposed to 0.27 times the normal limit for 24 hours before acquiring a body burden equal to a normal residual body burden. If the exposure were to be for 96 hours (4 days), the predicted limit would be 0.12 times the normal limit.

As the period of continuous exposure increases, the curves for $F_{p/r1}$ (no previous exposure) approach that for $F_{p/r2}$ (previous normal exposure). This variation of the model is not suitable for substances with half-lives less than about ten hours, because the normal residual body burden is virtually zero for these substances, and the model cannot be applied.

selection of predictive criterion

Peak body burden was selected as the criterion for general use in this model for predicting equal protection. As indicated above, the residual body burden is less suitable because it becomes zero for substances with short half-lives.

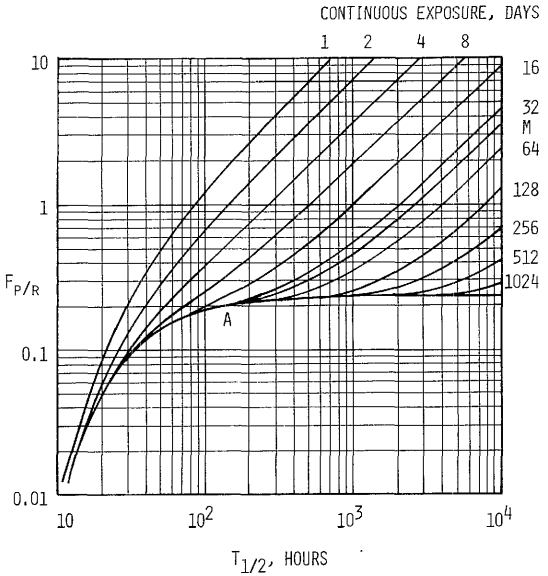


Figure 8 — Adjustment factor ($F_{p/r}$) equating continuous peak to normal residual body burden, as a function of substance half-life ($T_{1/2}$).

Use of the average body burden as criterion implies that the area under the curve for a special exposure schedule (as shown in Figure 2) must be no greater than the comparable area for a normal exposure schedule. The area under either curve in Figure 2 is a function only of total exposure time, and not of the schedule. Thus, any adjustment factor based on average body burden, B_a, as criterion will be unity for any two exposure schedules which have equal total exposure hours during equal time periods. This makes B_a unsuitable as a criterion with this model.

other applications of the model

In the discussions up till now, only inert gases and vapors have been considered. The model may also be applied to particulates and reactive gases and vapors.

particulates

The model as applied to particulates is analogous to its application to inert gases and vapors, with one exception; deposition of particulates in the body is presumed to occur at some linear rate proportional to air concentration. However, clearance of

particulates is presumed to be first-order exponential. The equations describing these actions are quite similar to equations 1 and 2, as follows:

$$\text{For uptake: } B_t = (CLf/k)\ (1 - e^{-kt}) + B_o(e^{-kt}) \quad \textbf{(12)}$$

$$\text{For clearance: } B_r = B_t(e^{-kt_r}) \quad \textbf{(13)}$$

in which

L = flow rate of air to the body (volume/time);
f = fraction of particulates deposited;
k = clearance rate of deposited particulates [$k = (\ln 2)/T_{1/2}$]; and the other symbols are as described in equations 1 and 2.

The retention of inhaled particulates has traditionally been considered to vary directly with their concentration in air. Models for such retention[17,18] are rate-independent of the air concentration of particulates. Therefore, assumption of a linear deposition rate appears valid.

The assumption of first-order clearance is more tenuous. The lung clearance rate apparently varies depending on the magnitude of lung burden, although there is no general agreement on this point.[17] It is thus not definite that clearance follows a single exponential,[17] although half-lives for particulate clearance have been published.[19] Because of the uncertainty of the half-life or half-lives for body clearance of any particulate substance, use of the worst case would seem to be prudent in using the model for adjusting particulate limits to predict equal protection.

When the model is applied to short exposures to particulates at high concentrations, there is the implicit assumption that the predicted allowable higher concentration limit is not so high as to overwhelm the deposition or clearance mechanisms of the body. This can occur[17] at very high concentrations, and application of the model to particulates is limited to this extent.

reactive gasses and vapors

The equations for uptake and excretion of reactive gases and vapors, using the one-compartment model, are

$$\text{For uptake: } B_t = CWK\,[1 - e^{-(k_1+k_2)t}]\,[k_1/(k_1+k_2)] + B_o[e^{-(k_1+k_2)t}] \quad \textbf{(14)}$$

$$\text{For excretion: } B_r = B_t[e^{-(k_1+k_2)t_r}] \quad \textbf{(15)}$$

in which k_1 is the uptake/excretion rate by respiration, k_2 the rate by metabolism, and the other symbols as described in equations 1 and 2.

Again, when F_p is calculated, the additional factor, $k_1/(k_1+k_2)$, cancels, and F_p is identical to that for inert gases and vapors, except that the effective half-life is described by k_1+k_2 rather than by k alone. That is, $k_1+k_2 = (\ln 2)/T_{1/2}$. Use of the prepared curves, such as Figure 3, to determine F_p, would require knowledge of the effective half-life of a substance or use of the worst case.

The model does not appear amenable to deriving adjustment factors for exposure to primary irritants or allergens. The actions of these substances appear to be based on such a small local compartment, as contrasted to the entire body, that the predicted equal protection would not apply.

limitations of the model

It must be recognized that the body is not an homogenous mass, as assumed in the one-compartment model. There are at least two compartments which should be considered, the lung-arterial blood system, and the individual target tissue. The two-compartment model[15,20] provides more precision in simulating body mechanisms, but is correspondingly more complex and thus not as widely used in modeling uptake and excretion.

While the prediction capability of this model is thus limited by the drawbacks of the one-compartment model, there are practical circumstances which minimize these drawbacks. First, many of the body tissues which are important targets for inhaled substances ("critical" tissues) are highly perfused,[21] and the concentration of the contaminant in these tissues may follow that of the arterial blood closely, thus in effect becoming part of the lung-arterial blood compartment. The opposite case is the critical tissue in which the build-up of contaminant is extremely slow, compared to the buildup in the rest of the body. In such a case, the remainder of the body, or more specifically the arterial blood, may be assumed to reach saturation relatively quickly and remain at a virtually constant concentration. In effect, the body (except for the critical tissue) becomes part of the ambient environment, and the critical tissue becomes the one-compartment body.

determination of substance half-life

Effective half-lives of substances are very difficult to determine precisely, because of the complex manner in which many substances behave in the body. A major complicating factor is that different parts of the body take up and excrete substances at different rates. Nevertheless, effective half-lives for human uptake and excretion have been determined for many substances, and several lists have been compiled.[11,19,22] It would be useful if an exhaustive list were compiled. Where available, these half-lives can be applied to the model, and where the half-life of a particular substance is unknown, the worst case may be used.

When dealing with inert gases and vapors, two half-lives may be known: that in the body as a whole, and that in a critical tissue. If both are known, the value giving the lesser F_p should be used; otherwise, the worst case. In dealing with particulates, the half-life for clearance by all mechanisms should be used if known; otherwise, the worst case. With reactive gases and vapors, the half-life used should account for both metabolism and respiration. If this is unknown, the worst case should be used. Published half-lives for substances in the body do not always take into account the variation of half-life with body compartment, but may represent a "mixed" half-life averaging the half-lives of more than one compartment. Such half-lives may not validly be used with any model when the half-lives of the substance involved vary widely in different body compartments.

comparison of model to published data

Many studies have described bodily uptake and body burdens acquired from exposure to substances in air under particular circumstances. Most of these data deal with quantifying uptake and burdens, and so are not suitable for confirming the derived model's predictions, since the model makes no attempt to quantify body burdens in absolute terms. Rather it compares ratios of predicted peak body burdens acquired at equilibrium under two different exposure schedules. Such specific studies are rather rare; however, there are some. Data from these studies have been compared to the model's predictions in detail elsewhere,[22] and are summarized here.

In one study,[23] 54 human volunteers were exposed to 200, 100 and 20 ppm trichloroethylene (TCE) in the air for periods of 7.5, 3, and one hours daily until body equilibrium was reached. The relative observed TCE peak body burdens resulting from these exposures were compared to those predicted by the model. Observed and predicted ratios, based on breath concentrations of TCE, coincided precisely at the 200 ppm concentration, quite closely at the 100 pm concentration, and less so at the 20 ppm concentration. [22] In another study, groups of men were exposed to 100 ppm of methylene chloride in air for two hours and for four hours.[24] The ratios of peak body burdens predicted by the model were identical to observed values, as measured by blood and breath concentrations of methylene chloride.

Human volunteers were exposed to 100, 200 and 494 ppm of carbon monoxide in air for several hours.[25] Equal body burdens, as measured by COHb concentrations, were observed to occur with 8 hours of exposure to 100 ppm, 2.6 hours to 200 ppm and 0.9 hours to 494 ppm. The model predicts, from Figure 6 or equation 9, equal body burdens from exposure to 100, 200 and 490 ppm for 8, 2.6 and 0.9 hours respectively. Human volunteers were exposed to a varying carbon monoxide concentration of from 50 to 1,000 ppm in air in 15-minute increments for 2 1/2 hours, and to 50 ppm carbon monoxide in air for 8 hours.[26] The ratio of the COHb accumulation from the 8-hour exposure to that from the incremental exposure was observed to be 0.18. The ratio predicted by the model (equation 6) was 0.16.

Many more such comparisons are of course needed before the area of validity and limitations of the model are adequately defined.

concluding remarks

A model has been developed for adjusting occupational exposure limits of air contaminants to unusual work schedules. The model takes into account the biological uptake and excretion mechanisms of the body as described by the one-compartment model. Graphs have been developed for determining adjustment factors for several unusual exposure schedules, and a general formula is provided for other situations.

The model is unique in that it provides a worst-case adjustment factor for use when the half-life of a particular substance in the body is unknown. As with any model, it should be used only under medical supervision until its area of application and its limitations are established.

The model operates independently of the TLVs (or PELs), and its application is not affected by any changes to these values which may occur as new evidence of toxicity or safety is developed.

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