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Exposure Limits for Unconventional Shifts: Toxicokinetic and Toxicodynamic Considerations

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Adjustment factors (AF) for inhalation exposure to chemical agents during unconventional work schedules were derived on toxicokinetic bases. AFs depend on the half-life of the agent and on the work schedule. Because they are grossly affected by cumulation, AFs were calculated for steady-state conditions. They were based on the following measures of chemical body burden: (1) end-of-shift biological level as used previously by other investigators; and (2) areas under the curves, AUC_{exp}, AUC_{day}, and AUC_{week}, which correlate with average biological levels during the shift, work day, and work week, respectively. The dependence of AFs on the half-life was studied on 50 possible work schedules using agents with a half-life of 1 hr to 2 years. Based on the data, simple equations suitable for field conditions were derived for determination of AFs. Since AFs based on individual measures of body burden are not the same, the pharmacodynamics of the toxic endpoint should be considered when selecting the measure of body burden and the half-life for AF determination. Am. J. Ind. Med. 31:744–755, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: occupational exposures; TLV; toxicokinetics; unconventional work shifts; body burden; chemicals

INTRODUCTION

Occupational exposure limits, such as TLV, MAC, and PEL, are time-weighted averages (TWA concentrations) of chemical air pollutants which are meant to provide health protection in work places with a conventional work schedule of 40 hr/week (i.e., 5 consecutive days of 8-hr shifts). For a short time, the TWA can be exceeded. The permissible excursion concentration is defined either by short-term excursion limits or by excursion factors derived on a statistical basis (i.e., on the probability that the TWA would be maintained) considering the toxicodynamics and seriousness of the health effect.

Application of TWA exposure limits to industrial operations with extended shifts and unconventional shift cycles has been questioned. A formula for adjusting TWA exposure limits for unconventional shift cycles was first proposed by Brief and Scala [1975]. Their reduction factor, RF, is based on the ratio of exposure duration to nonexposure duration per week:

$$RF = \frac{40}{N} \cdot \frac{168 - N}{128}$$

where N denotes the number of hours for which the worker is exposed during an unconventional work week. Numbers 40 and 128 represent the hours of exposure and nonexposure over a week of conventional shifts, and 168 represents the total number of hours per week.

Toxicodynamic Approach

OSHA recognized that development of the adverse effect plays an important role in the safety of exposure during unconventional shifts [OSHA, 1976]. Based on simplified toxicodynamic assumptions, OSHA regulators pooled the chemical air pollutants into four categories: (1) *ceiling* (irritants and agents with PEL based on technologic feasibility), which does not require exposure adjustment for

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unconventional work schedules; (2) *acute*, which requires the following adjustment for daily exposure:

$$\text{Adjusted PEL} = \text{PEL}\,\frac{8}{n}$$

where n denotes the number of exposure hours (unconventional shift duration); (3) *cumulative*, which requires the following adjustment for weekly exposure:

$$\text{Adjusted PEL} = \text{PEL}\,\frac{40}{N}$$

where N denotes the number of exposure hours during an unconventional work cycle; and **(4) *acute and cumulative***, which requires adjustment for daily or weekly exposure, depending on which provides stronger protection.

Toxicokinetic Approach

Mason and Dershin [1976] recognized that the rates of rising and declining concentrations of inhaled agents in the body affect systemic toxicity; they related the chemical body burden to the biological levels of the chemical agent at the end of the last shift of the work cycle. They also acknowledged the dependence of the safety factor on the half-life of the uptake and elimination of the agent. Based on toxicokinetics, they proposed a multiexponential equation for predicting cumulation of the inhaled agents in the body over an unconventional work cycle. Hickey et al. [1977, 1979, 1980] and Roach [1978] further elaborated on these ideas and applied the toxicokinetic concept to a variety of working situations. Andersen et al. [1987] used the physiologically based pharmacokinetic model to evaluate the occupational risk of exposure to some organic solvents. The toxicokinetic models were comprehensively reviewed by Paustenbach [1985].

Measures of Chemical Body Burden

The systemic effects of xenobiotics (toxic substances, drugs) correlate better with their internal dose than with their external dose. The measure of internal exposure can either be the concentration of the agent in the blood, or the area under the curve (AUC) depicting the concentration of the inhaled agent in the blood during and after exposure.

The adjustment factor for individual agents should be based on the measure exhibiting the best correlation with the toxic endpoint. Some adverse effects, such as diminished vigilance, analgesia, and imtation, are related to the biological levels at the target site and thus to the highest concentration of the agent (or metabolite) reached in the blood. The end-of-shift biological level has therefore been used as the criterion for establishing the safety factors for these agents. The majority of toxic endpoints, such as carcinogenicity [EPA, 19921 and hepatotoxicity, are related to the AUC during exposure (AUC_{ss}). AUC_{ss} reflects the average biological level during exposure. Finally, systemic adverse effects of agents with a very long half-life may best correlate with the dose related to AUC over the work cycle (AUC_{week}). An example is the adverse effect induced by saturation of binding sites, as in the case of nephrotoxicity induced by exposure to some heavy metals [Lauwerys and Bernard, 1987].

Figure 1 shows the dependence of the measures of internal exposure-concentration in blood and AUCs—on the duration of exposure and on the half-life of the agent. The sketch presented in Figure 1 (top) clearly shows that biological levels of agents with a short half-life level off during a conventional shift and remain unchanged if the shift is extended. By contrast, the AUC increases with the exposure duration. The bottom sketch shows that the biological levels and AUCs of agents with a long half-life slowly rise when the exposure is extended.

This paper derives and compares the adjustment factors for prolonged exposures to agents with health effects related to biological levels and AUCs. Exposures permissible during a conventional work schedule, multiplied by the derived adjustment factors, represent a toxicokinetic equivalence to exposures permissible during a conventional work schedule.

METHODS

Equipment

This work involved the use of an IBM personal computer and Matlab software (The Math Works, Natick, MA, 1992).

Mathematical Approaches

It is assumed that the airborne concentration of the agent during the shift is constant, and that the permissible concentrations are so low that first-order kinetics apply to all processes, including metabolism and binding. According to our experience, most TWA exposure limits comply with these assumptions [ACGIH. 1992; Commission for Investigation ... , 19951.

Single exposure

At low inhalation exposures, when first-order kinetics apply, the rise and decline of biological levels of the agents during and following exposure are described by two exponential functions.

The rising of the biological level is described by Equation (1):

$$Z(t) = Z_1 e^{-kt} + C(1 - e^{-kt}) \qquad (1)$$

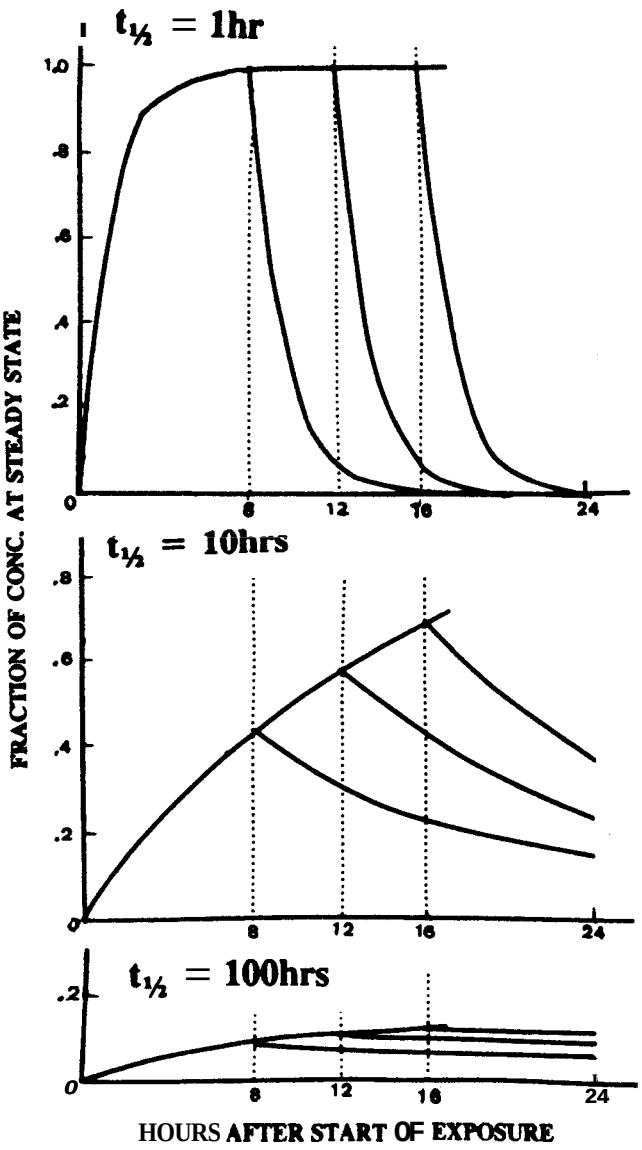

FIGURE 1. Schematic picture of dependence of biological levels, AUC_{exp}, and AUC_{post} on the half-life of the agent and duration of the exposure. Biological levels, expressed as fractions of the steady state levels, are plotted against time. In the examples given, the exposures lasted 8, 12, or 16 hr. The dotted lines separate AUCs during exposure (AUC_{exp}) and following exposure (AUC_{post}).

The declining of the biological level following the offset of exposure is described by Equation 2:

$$Z(t) = Z_2 e^{-kt} \tag{2}$$

In these equations, Z(t) denotes biological levels as a function of time t, Z_1 is a possible residue from the previous exposures, Z_2 is the biological level at the end of exposure (Fig. 2), and e is the base of the natural logarithm. C, which is directly related to the average exposure concentration (TWA), represents the maximum biological level of the agent which can be reached at the given airborne concentration. The rate constant k is related to the elimination half-life, $t_{1/2}$:

$$k = \frac{\ln 2}{t_{1/2}} \tag{3}$$

If the duration of the shift with exposure is denoted by x_1, and the duration of the post-shift period without exposure is denoted by y_1, Equations 1 and 2 can be rewritten as follows to calculate the biological level at the end of the shift:

$$Z_2 = Z_1 e^{-kx_1} + C(1 - e^{-kx_1}) \tag{4}$$

and at the end of the post-shift period:

$$Z_3 = Z_2 e^{-ky_1} \tag{5}$$

Intermittent exposure

Biological levels at the end of the shift on the i^{th} day of the work cycle (Z_{2i}) and before the next shift (Z_{2i+1}) can be calculated using Equations (6) and (7). End-of-shift level:

$$Z_{2i} = Z_{2i-1} e^{-kx_i} + C)(1 - e^{-kx_i}) \tag{6}$$

Prior-shift level:

$$Z_{2i+1} = Z_{2i} e^{-ky_i} \tag{7}$$

Biological levels during intermittent exposures can be calculated for any day by using Equations (6) and (7) in sequence, starting with i = 1 and substituting the parameters for the first work day, then with i = 2 and substituting the parameters for the second work day, and so forth, until, for the last day of the work cycle, i = n, where n denotes the number of days in the work cycle.

If the circadian cycle is maintained, $y_i = 24 - x_i$. The fluctuation of biological levels during a conventional work week is pictured in Figure 2. To account for weekends and other days without exposure, C for such days equals zero.

Steady state

If the cycles of intermittent exposures are repeated, cumulation rate over repeated work cycles declines until the steady state is reached. At that time, the biological levels at the beginning and end of the cycle are the same ($Z_{2n+1} = Z_1$) and the cycle of biological levels is repetitious.

Biological levels in a cycle composed of n days is described by a set of 2n linear equations with 2n unknowns denoted by Z_i. Numerical solution of these equations is easy when using a computer [Mason et al., 1976; Hickey et al.,1977; Roach, 1978]. We used the Matlab program because of its graphical capabilities.

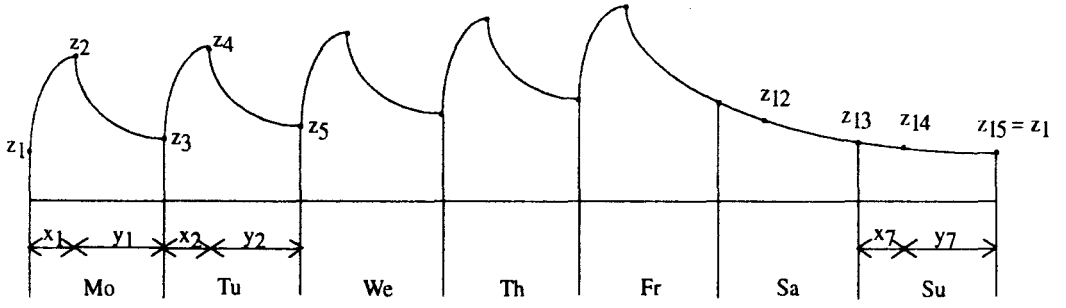

FIGURE 2. Schematic representation of an intermittent weekly exposure. The symbols, also used in the equations, are explained in the text.

Areas under the curves

Once the biological levels at steady state have been calculated, the areas under the curves **(AUC)** depicting the rising and declining of biological levels can be calculated by integrating Equations (1) and (2). The **AUC** during any shift in the work cycle (denoted by subscript i) is:

$$AUC_{exp_i} = {}_0\int^{x_i} [Z_{2i-1}e^{-kt} + C(1 - e^{-kt})]\,dt$$

$$= Cx_i + \frac{Z_{2i-1} - C}{k}(1 - e^{-kx_i}) \quad (8)$$

Similarly, **AUC** during the resting post-shift period is:

$$AUC_{post_i} = {}_0\int^{y_i} Z_{2i}e^{-kt}\,dt = \frac{Z_{2i}}{k}(1 - e^{-ky_i}) \quad (9)$$

The daily areas under the curves, $AUC_{day,i}$, are calculated as the sum of AUC_{exp_i} and AUC_{post_i}. The weekly areas are calculated as the sum of daily **AUCs.** The areas are directly related to the mean (TWA) biological levels during the shift (AUC_{exp}), during the day (AUC_{day}), and during the work week (AUC_{week}).

Adjustment Factor

To determine the bioequivalents of exposures during conventional and unconventional shifts, four measures of body burden calculated for steady-state conditions were compared: (1) ***peak*** biological levels (end-of-shift levels); (2) average biological levels during the shifts **(AUC_{exp});** (3) average biological levels during the day (AUC_{day}); and **(4)** average biological levels during the week (AUC_{week}). The adjustment factors **(AF)** were determined as ratios of values of individual parameters calculated for conventional and unconventional shifts. Unless indicated otherwise, the AFs were calculated by dividing the biological level (or AUC) derived for the 5th day of the conventional work cycle by the same parameter derived for any day of the unconventional schedule. To determine whether the AFs based on the last shift in the conventional cycle are the most critical, the ratios of the parameters were determined on a daily basis. **Since** AFs **are** ratios of linear functions, they **are** independent of exposure concentrations **and,** for simplicity, C = 1 was used in calculation.

For unconventional work schedules, the exposure bioequivalent to the permissible exposure limits is calculated by multiplying the permissible exposure concentration (e.g., PEL, TLV, or **MAC)** by the adjustment factor.

RESULTS AND DISCUSSION

The calculations of adjustment factors presented above are a refinement of previously published studies proposing

TABLE I. Weekly Work Cycles Used in the Examples. Duration of **Shifts** in Hours

Week	work							
day:	**schedule**	I	II	III	IV	V	VI	VII
		Conventional schedule						
		8	8	8	8	8	0	0
		Unconventionalschedule						
40 hrs/week	A	10	10	10	1	0	0	0
	B	0	10	10	10	10	0	0
	C	12	8	0	12	8	0	0
	D	8	12	0	8	12	0	0
	E	0	0	16	1	6	8	0	0
	F	0	0	8	16	16	0	0
	G	16	0	0	1	6	8	0	0
48 hrs/week	H	0	12	12	12	12	0	0
	I	12	12	0	12	12	0	0
	J	0	0	16	16	16	0	0
	K	16	0	16	0	1	6	0	0
64 hrs/week	L	16	16	0	16	16	0	0
	M	0	16	16	16	16	0	0

The between-shinperiods = 24 – shift hours

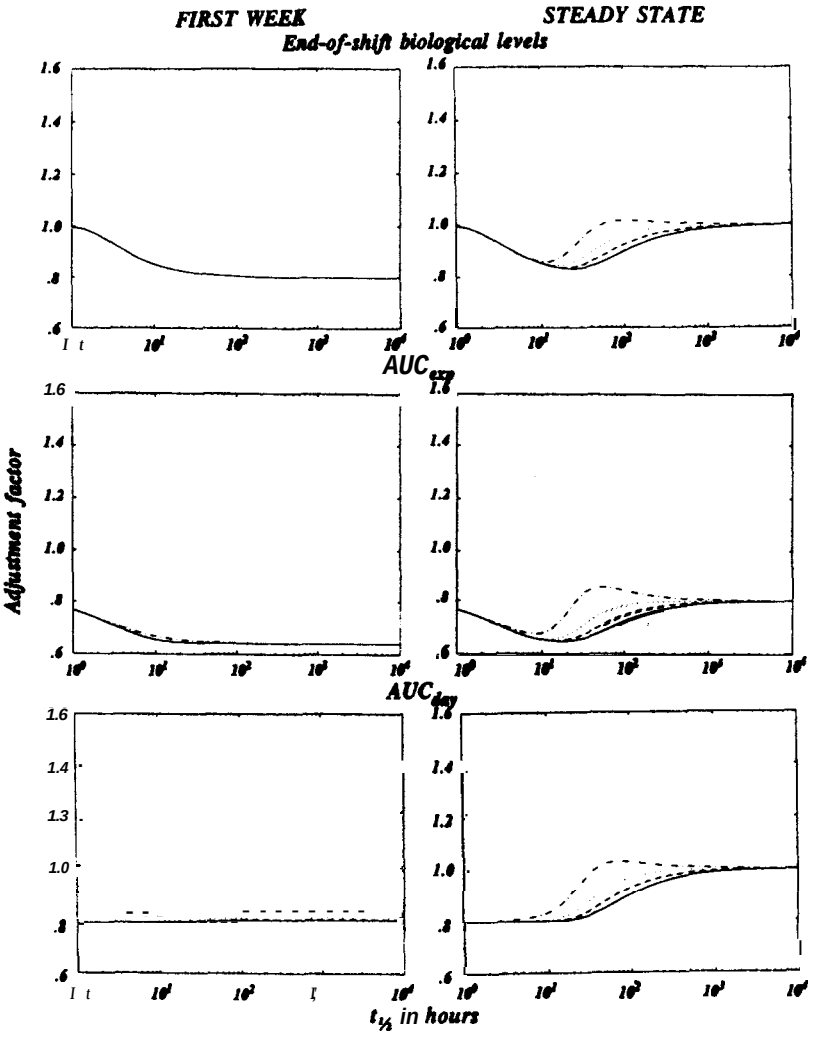

FIGURE 3. Dependence of adjustment factors (AF) on the half-life ($t_{1/2}$) of the agents. Comparison of AFs for the first work week with AFs at steady state. AFs, based on biological levels at the end of the shifts, AUC_{exp}, and AUC_{day}, are calculated for the first work week (left) and for the steady state (right). The unconventional work week consists of four consecutive days with 10-hr shifts followed by three days off. AFs for the first shift are calculated as a ratio of the values calculated for the first shifts of the conventional and unconventional work week. AFs for other shifts are similarly calculated. 1st unconventional shift: _._._._; 2nd unconventional shift: . . . . . ; 3rd unconventional shift: - - - - -; 4th unconventional shift: _____.

exposure adjustment for unconventional work cycles based on the toxicokinetic prediction of end-of-shift biological levels at steady state: (1) the effect of cumulation on AFs is observed by comparing the AFs derived for the first work cycle and for the work cycle at steady state; (2) calculation of biological end-of-shift levels, AUC_{exp}, and AUC_{day}, for each shift of the work cycle, allows identification of the shift inducing the largest body burden during conventional and unconventional work schedules (reference shift and critical shift, respectively); (3) the AUCs during the shift (AUC_{exp}), during the work day (AUC_{day}), and during the work week (AUC_{week}), which correlate with TWA biological levels during the shift, day, and week, respectively, are considered as alternative bases for determination of AFs; and (4) the measures of body burden used for determination of AFs are related to the toxic endpoint of the agent.

Our conclusions on the effects of cumulation, measures of chemical body burden, and work schedules on AFs of agents with a different half-life are based on the study of 50 different work schedules. The typical findings are demonstrated

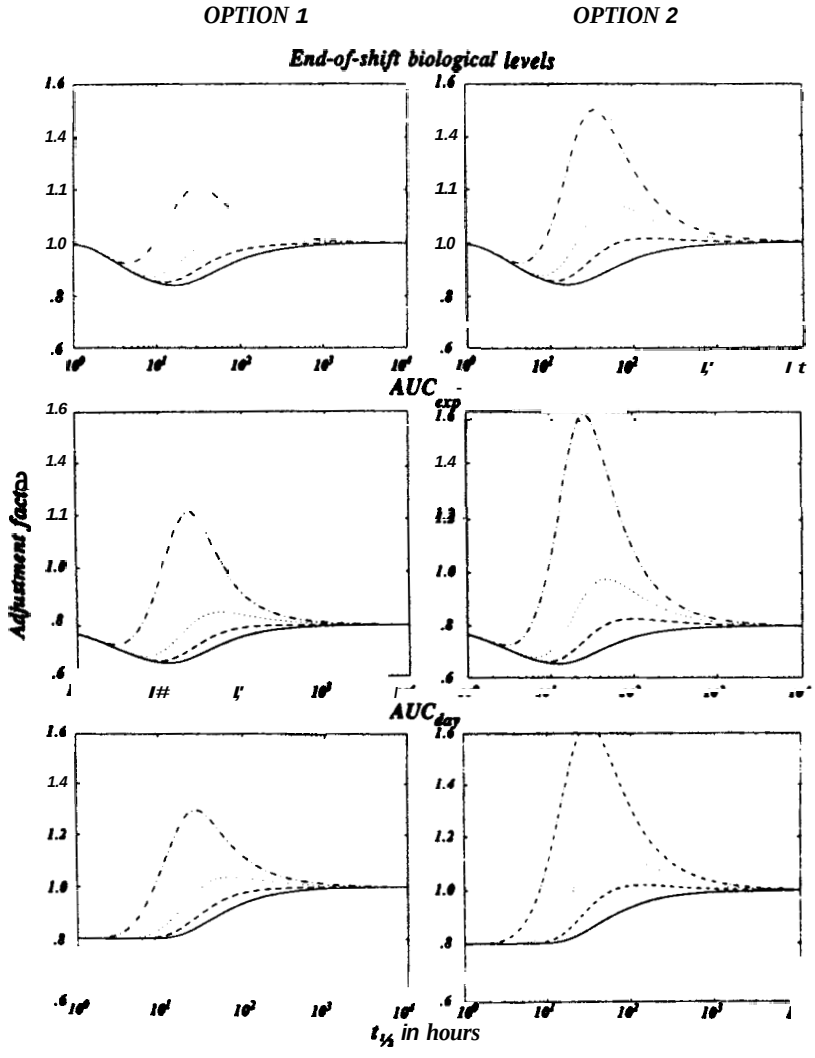

FIGURE 4. Additional options for calculation of adjustment factors. As in Figure 3, the example uses four 10-hour shifts, but the work week starts with a day off (work schedule B in Table I). Option 1 *(left)*: AFs for all three measures of body burden are ratios of values calculated for the second shift in the conventional work week and first shift of the unconventional work week, and so on, as indicated by columns in Table I. *Option* 2 (right): All AFs are ratios of values calculated for the last shift of the conventional work week and indicated shifts in the unconventional work schedule. 1st unconventional shift: _·_·_·_; 2nd unconventional shift: . . . . . ; 3rd unconventional shift: - - - -; 4th unconventional shift: ——.

on 13 examples whose schedules are shown in Table I. In these examples, the 7-day cycles and circadian rhythm are maintained so that the cycle duration $W = 168$ hr and $y_i = 24 - x_i$.

Effect of Cumulation on Adjustment Factors

The effect of cumulation on AF for agents with a different half-life is demonstrated in Figure 3 by using an unconventional work cycle of four consecutive days with 10-hr shifts followed by three days off (schedule A in Table I). AFs for all shifts during the first work week are almost the same. They indicate an increased risk of prolonged exposure to slowly eliminated agents.

During repetitious work cycles, cumulation reduces the effect of shift prolongation. At steady state, AFs for individual shifts differ, the most apparent differences being exhibited by agents with a half-life of 10–200 hr. In the

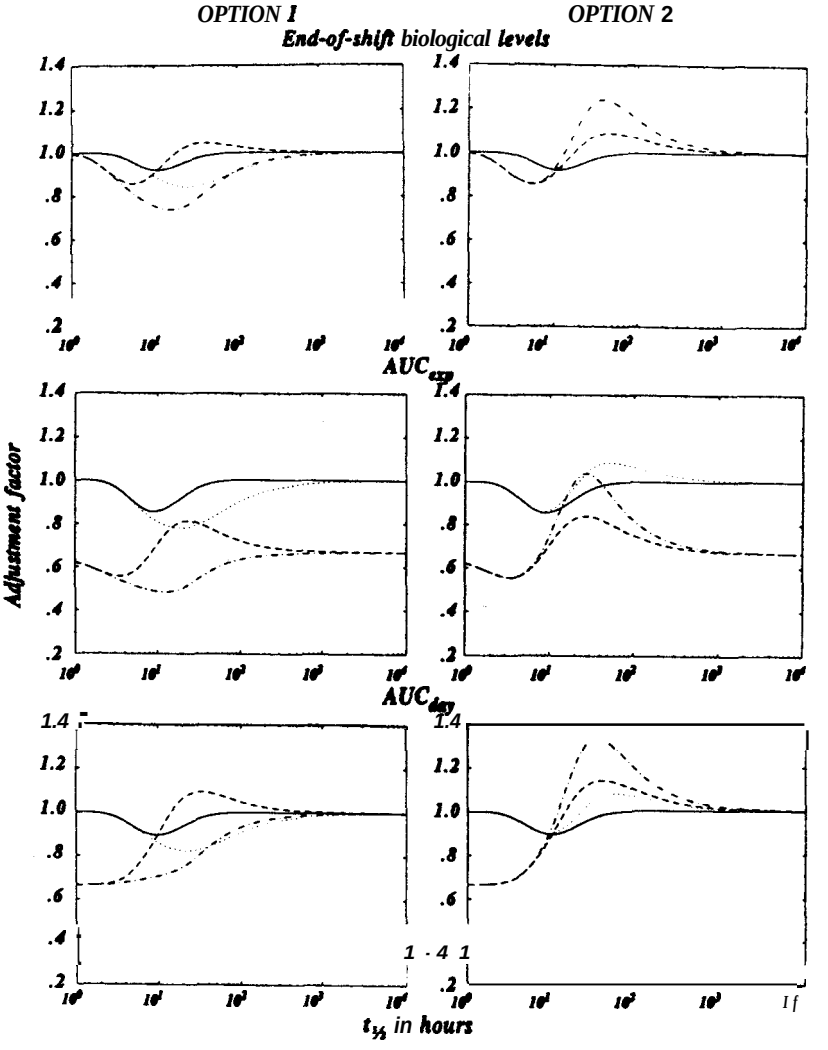

FIGURE 5. Finding the critical shift. This example of combination of 8-hour and 12-hour shifts (work schedule C in Table I) documents that *the* last (fourth) shift in the unconventional work schedule is not always the critical shift requiring the largest adjustment. The AFs are calculated for Option 1 (lefl side) and Option 2 (right side). For further explanation see Figure 4.

given example, when shifts of equal duration are on consecutive days, the largest adjustment is indicated for the last shift of the work week (full lines in Fig. 3) and the smallest adjustment is indicated for the first shift (broken lines in Fig. 3). AFs for agents with very long half-lives are the same.

In the example, no exposure adjustment is indicated for slowly eliminated agents if the toxic endpoint is related to the end-of-shift biological level or to the daily **TWA** biological level (AUC_{day}). For agents with a very short half-life, no adjustment is needed if the toxic endpoint is related to the end-of-shift biological level, but an adjustment of 0.8 (8/T) is indicated for agents with a toxic endpoint related to the TWA levels (AUC_{exp} and AUC_{day}). The largest adjustment is needed for all agents with a toxic end-point related to AUC_{exp}. In the given example with 40-hr work weeks (the same as in conventional work week), **AF** based on AUC_{week} equals 1.

Conclusions

With the exception of agents with a short half-life, the AFs calculated for the first work cycle are smaller than those calculated for the steady state. As a result of cumulation, biological levels (and **AUCs)** increase, and the differences between conventional and unconventional work schedules diminish. In an occupational setting, adjustment for repetitious exposures is crucial. Therefore, the rest of this

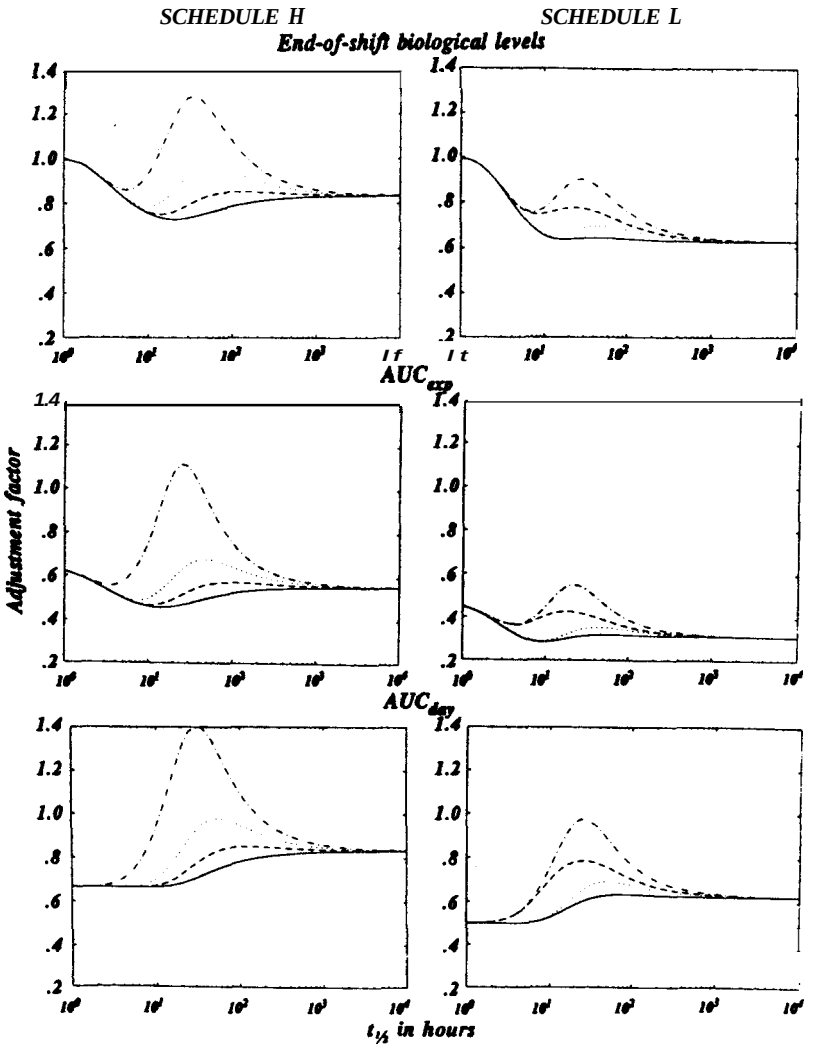

FIGURE 6. Extended weekly working hours. Option 2 was used to calculated AFs for a 48-hour work week consisting of four 12-hour shifts on consecutive days and a 64-hr work week consisting of four 16-hr shifts with a day off after the second shift (Schedule H and L In Table I). Note that all AFs for slowly eliminated agents equal 40/W, the exception being AUC_{exp}. 1st unconventional shift: _.-._.-._; 2nd unconventional shift: . . . . . .; 3rd unconventional shift: - - - - -; 4th unconventional shift: _____.

discussion concentrates on the AFs for steady-state conditions.

Reference Shift

Figure 3 relates four shifts in the unconventional work week to the first four conventional shifts. The last (fifth) shift of the conventional work week (which exhibited the highest body burden) was not used for determination of AFs.

There are two other options for AF determination: In Option 1, if the same unconventional work week starts with 1 day off (work schedule B in Table I), the AFs for the first unconventional shift are based on the second conventional shift, etc. as indicated by the columns in Table I. In this option, the first conventional shift is not used for determination of AFs but the last conventional shift is used for calculation of AFs for the last unconventional shift. Option 2 uses the last (fifth) shift of the conventional work week as the reference shift; this shift exhibits the highest values for all measures of chemical body burden (Fig. 2).

In Figure 4, AFs are compared using Option 1 (left side) and Option 2 (right side). In the given example, the largest adjustment is indicated for the fourth (last) unconventional shift, regardless of the body burden measure or option used. Contrary to work schedule A (Fig. 3), the AFs exceed 1 for the first two shifts of the workweek if the agent has a

TABLE II. Estimation of Adjustment Factors Based on Four Measures of Body Burden[a]

Parameters	$t_{1/2}$ < 4 hrs AF_1	Largest reduction $t_{1/2}$ (hrs)[c]	AF_2	Inflection[b] $t_{1/2}$ (hrs)	$t_{1/2}$ > 20 days AF_3
Biol. levels	1	6–18	½(8/T + 40/W)	80 — 100	40/W
AUC_{exp}	8/T	3–14	8/T · 16(T + t)	70 → 100	8/T · 40/W
AUC_{day}	8/T		8/T	50 — 100	40/W
AUC_{week}	40/W		40/W	None	40/W

[a]Agents are characterized by half-life ($t_{1/2}$). Work schedules are based on weekly work cycle and circadian cycle.
[b]Indicates the half-lie of agents for which AF = (AF_2 + AF_3)/2. The inflection point depends on the work schedule. It appears at the shorter $t_{1/2}$ if a day off is inserted between the prolonged shii.
[c]Indicates the range of half-life of the agents with the smallest AF.
AF = adjustment factors. T = duration of the longest shift in the week (in hours). t = duration of the shii preceding or following the longest shift. fall s h i i are of the Same duration, then t = T. W = number of working hours/week.

half-life in the range of 10–200 hr. Comparison of Figures 3 and 4 indicates that the smallest adjustment is needed if AFs are based on Option 2 (last conventional shift). AFs for schedules A and B are the same when Option 2 is used.

Conclusions

In an unconventional work week, some shifts exhibit an AF larger than one, some an AF smaller than one, depending on the work schedule and half-life of the agent. Permissible exposure limits comprehend safety of the last shift in the conventional work week. This shift exhibits the highest values of the end-of-shift biological levels as well as TWA biological levels (AUC_{exp} and AUC_{day}). Therefore, use of the last shift of the conventional work schedule as a reference shift is permissible. It is unambiguous in cases with complex, irregular work cycles. The last shifts were also used as a reference shift in the previous studies [Mason et al., 1976; Hickey et al., 1977, 1979; Roach, 19781.

Critical Shift

The critical shift in the work week is the shift which requires the largest adjustment, i.e. the smallest AF. In the previous schedules, when shifts of equal duration occurred on consecutive days, the smallest AFs were indicated for the last shift in the work week. This was not always the case if the schedule consisted of shifts of unequal durations with a day off between. An example is shown in Figure 5, using work schedule C in Table 1. In this example. consisting of two 12-hr shifts each followed by 8-hr shifts and a day off, all three body burden measures require a larger exposure adjustment for the first and third shifts than for the last (fourth) shift. In this example, which maintains the 40-hr work week, no exposure adjustment is indicated for any shift with exposure to agents with a half-life longer than 200 hr and toxic endpoint related to end-of-shift biological level, AUC_{day} and AUC_{week}. A significant exposure reduction, however, is indicated for the first and third shifts with exposure to agents with a long half-life and toxic endpoint related to AUC_{exp} (AF = 8/12 = 0.666).

Conclusion

The last shift of an unconventional work week is the critical shift if the work schedule consists of shifts of equal duration on consecutive days. If the shift duration is unequal or a day without exposure is inserted between working days, the longest shift (or the shift prior to the day off) may be the critical shift. For agents with a long half-life, the AFs for all shifts in the cycle approach the same value, with the exception of AF based on AUC_{exp}. The extent of adjustment varies for individual measures of body burden and work schedule.

Effect of Weekly Work Hours on AFs

Figure 6 presents two examples of work weeks with 48 hr (four 12-hr shifts on consecutive days) and 64 hr (four 16-hr shifts with a day off after the second working day), respectively (Schedules H and L in Table I).

Conclusions

The shift duration mainly affects AFs of agents with a short half-life, while AFs for agents with a long half-life are affected by the number of working hours per week (AF = 40/W). AFs for agents with a half-life of 10–200 hr must be calculated individually. AFs based on AUC_{week} are always equal to 40/W, regardless of the working schedule or the half-life of the agent.

Estimation of Adjustment Factors

The calculation of AFs, described above, is complex, and difficult to perform in field conditions. To simplify the calculation, essential AFs were estimated based on curves similar to those shown in Figures 4–6. Curves calculated for 50 unconventional work cycles were analyzed. Table II shows the formulas for estimation of AFs for agents with a very short half-life, $t_{½}$ <4 hr (AF_1), a very long half-life, $t_{½}$ >20 days (AF_3), and those requiring the largest adjustment (AF_2). The table also shows that the largest adjustment is needed for agents with a half-life of 3–18 hr. The inflection point of the half-life provides guidelines whether AF_2, AF_3, or the mean of both should be used.

TABLE III. Exposure Limits for Unconventional Shifts: Comparison of Calculated and Estimated Adjustment Factors[a]

	Short half-life				long half-life				Largest reduction			
Schedule[b]	Bil. level		AUCs 8/T		level and AUC_{day} 40/W		AUC_{exp} 8/T · 40/W		Biol. level ½(8/T + 40/W)		AUC_{exp} 8/T · 16/(T + t)	
					W = 40 hr							
	T = t = 10 hr											
A, B	1	1	.80	*.80*	1.00	1.00	.80	*.80*	.90	.84	.64	*.65*
	T = 12 hr, t = 8 hr											
C	1	*1*	.67	*.67*	1.00	1.00	.67	.67	.83	*.86*	.53	*.56*
D	1	1	.67	.67	1.00	*1.00*	.67	*.67*	.83	*.83*	.53	*.54*
	T = 16 hr, t = 8 hr											
E	1	1	.50	*.50*	1.00	*1.00*	.50	*.50*	.75	*.66*	.33	*.29*
F	1	*1*	.50	*.50*	1.00	1.00	.50	*.50*	.75	*.64*	.33	*.28*
G	1	*1*	.50	*.50*	1.00	1.00	.50	*.50*	.75	*.76*	.33	*.37*
					W = 48 hr							
	T = t = 12 hr											
H	1	1	.67	*.67*	.83	*.83*	.56	*.56*	.75	*.73*	.44	*.46*
I	1	*1*	.67	*.67*	.83	*.83*	.56	*.56*	.75	*.78*	.44	*.49*
	T = t = 16 hr											
J	1	*1*	.50	.50	.83	*.83*	.42	*.42*	.67	*.61*	.25	*.27*
K	1	*1*	.50	*.50*	.83	*.83*	.42	*.42*	.67	.75	.25	*.37*
					W = 64 hr							
	T = t = 16 hr											
L	1	*1*	.50	*.50*	.62	*.62*	.31	*.31*	.25	*.26*	.56	*.57*
M	1	*1*	.50	.50	.62	*.62*	.31	*.31*	.25	*.29*	.56	*.64*

[a] Estimated values (italicized numbers) were calculated using the above equations. The preceding (nonitalicized) numbers are values calculated as explained in text under Mathematical Approaches.
[b] Letters A-M denote work schedules of unconventional shifts as cited in text and shown in Table I. Other symbols are the same as in Table II.

Differences between calculated and estimated values, shown in 13 examples in Table III, indicate that the accuracy of the estimates meets the requirements of field studies.

Adjustment Factors in Other Studies

Table VI compares AFs derived in this paper with those derived by other investigators. Table VI shows that the AFs derived in this study, and those derived by Roach [1978], are significantly larger then the reduction factors proposed by Brief and Scala [1975]. Neglect of the toxicokinetic profile of the agent leads to overprotection. As expected, the AFs based on biological end-of-shift levels in this study agree with the values calculated by Roach [1978].

Adjustment factors for exposure reduction can be based on one of the four measures of body burden. The AF based on body measure best related to the toxic endpoint should be used. AFs derived for different measures of chemical body burden were compared with OSHA's recommendation [1976] for exposure adjustment based on an empirical toxicodynamic approach (Table VI). Adjustment factors based on biological end-of-shift levels of rapidly eliminated agents support OSHA's recommendation for agents with ceiling exposure limits. The adjustment factors based on the AUC_{day} support OSHA's recommendation for agents with acute toxic effect. These AFs should also be applied to carcinogens [EPA, 19921 which OSHA classifies as agents with exposure

TABLE IV. Half-lives of Organic Compounds

Compound[a]	$t_{1/2}$ of parent compound: Min	Hr	Days	Urinary metabolite	$t_{1/2}$ of metabolite: Hr	Days
Solvents, and other volatile, hydrophobic agents						
Benzene	25	2.5	1.25	Phenol	6	1.2
Enflurane	18	3.2	1.5	Fluoride		1.6
				Org. fluorine		3.7
Ethylbenzene	3	1.5	2	Mandelic ac.	5	1
Halothane	40	5	1.25	TFAA		2.33
n-Hexane	8	1.7	2.1	Hexanedione	14	
Isoflurane	9	2	0.73			
Methylchloroform	60	5	1.3	TCAA		3
				TCE	11	
MEK (ur)	30	1.35				
MIBK	20	1.25	0.25			
(ur)	4 0	7				
Perchloroethylene	15	4	4	TCAA		3.3
Styrene (bl)	30	12	3	Mandelic ac.	3.5	1.4
Toluene	26	3.7	3.2	Hippuric ac.	2	
				o-Cresol	3	
Trichloroethylene	20	3	1.25	TCAA		3
				TCE	19	
Xylene	60	20		Methylhip. ac.	3.6	1.25
Other organic agents, low volatile, hydrophilic						
Acetone	3	3.5				
(ur)		3.5				
Aniline	30			p-Aminophenol	3	0.4
DMF				MMF	3, 7	
Furfural				Furoic ac.	2	
Methanol (ur)		2.0		Formic ac.	2.25	
Phenol (ur)					3.5	
PCP (ur)						1.2;72

[a]Measured in exhaled air unless indicated otherwise. $t_{1/2}$ of industrial agents from ACGIH [1992]; $t_{1/2}$ of anesthetic agents from Holaday et al. [1979] and Fiserova-Bergerova [1992]. ur, urine: bl, blood.

TABLE V. Half-Lives of Metals and Other Inorganic Compounds

		Days			Months	Years
As	(urine)	1	3.5	8		
Cd	(blood)				3.6	10
	(urine)	0.5	2.7			10-30
Co	(blood)	0.5	2.7		2.0	
	(urine)				1.4	
F	(urine)	0.25				
	(bones)					1.5
Hg	(plasma)		10	28	3.5	
	(eryt.)		7	27	5.7	
	(urine)			40		
Pb	(blood)			40	6	40
	(urine)				1	20

$t_{1/2}$ from ACGIH, 1992.

TABLE VI. Comparison of Adjustment Factors in 4 Studies. Unconventional Weekly Cycles of 10-Hour Shifts on Consecutive Days and Between-Shift Periods of 14 Hours

Shifts per week	$t_{1/2}$ hrs	This paper: c_{exp}	AUC_{exp}	AUC_{day}	AUC_{week}	Roach	Brief & Scala	OSHA*
4	1	1.00	.77	.80	1.00	1.00	1.00	1.00[a]
	10	.85	.66	.80	1.00	.85	1.00	.80[b]
	1000	1.00	.80	1.00	1.00	.99	1.00	1.00[c]
	1	1.00	.77	.80	.80	1.00	.74	1.00[a]
	10	.85	.65	.80	.80	.85	.74	.80[b]
	1000	.80	.64	.80	.80	.80	.74	.80[c]
6	1	1.00	.77	.80	.67	1.00	.56	1.00[a]
	10	.85	.65	.80	.67	.85	.56	.80[b]
	1000	.67	.54	.67	.67	.67	.56	.67[c]

c_{exp}: Adjustment factor for agents with toxic endpoint related to biological end-of-shift level (instant toxicity). AUC_{exp}: Adjustment factor for agents with toxic endpoint related to time weighted average level during the shift (acute toxic@). AUC_{day}: Adjustment factor for agents with toxic endpoint related to time weighted average level during the day (subchronic toxicity). AUC_{week}: Adjustment factor for agents with chronic toxicity.

*Adjustment factors recommended for ceiling (a), acute (b), and chronic effects (c), respectively. (Independent of the half-life).

limits based on technologic feasibility. Adjustment factors based on the AUC_{week} support OSHA's recommendation for agents with chronic effects.

Determination of Half-Lives of Chemical Agents

The half-lives of organic compounds and of metals listed in BEI documentations [ACGIH, 19921 are shown in Tables IV and V, respectively. The half-lives of chemical agents can be determined experimentally from the elimination curves of the agent or its metabolite. The half-lives of volatile solvents can also be predicted from the physicochemical properties of the agent and the physiological parameters of the exposed subjects [Fiserova-Bergerova et al., 1974, 1980]. Half-lives of volatile hydrophobic solvents indicate triphasic uptake and elimination, with no half-life exceeding 4 days. The occupational exposure limits for some solvents are based on irritation or reduction of vigilance and other CNS functions. These effects are related to the fast compartment, that is, to the shortest half-life (Table IV). No exposure adjustment, therefore, is needed. However, if the toxic endpoint is related to the TWA biological

level during the shift, day, or week, the adjustment factor based on the appropriate AUC should be used. If the target toxic endpoint is not identified, the smallest AF should be used.

Table V shows very long half-lives for all metals. Therefore, an adjustment based on the AUC_{week} is appropriate. (AF = 40/working hours per week).

Significance of Exposure Adjustment for Unconventional Work Shifts

The work schedule is not the only factor affecting the chemical body burden. Dermal absorption and physical workload significantly increase the internal dose. Moreover, increased alveolar ventilation and increased tissue perfusion during strenuous physical activity result in shortening of the half-life [Fiserova-Bergerova, et al., 19801. The exposure limits are usually set for a light or moderate workload with minute ventilation of 20 L/min. Pulmonary ventilation doubles with a heavy workload. [Astrand, 1983; Fiserova-Bergerova 1995]. This means that the dose inhaled at a heavy work load can more than double, thus calling for adjustment by a factor of about 0.5. The same adjustment is most likely the largest exposure reduction required for an unconventional work schedule in an occupational setting. It is believed that the exposure limits have safety factors that afford protection during a heavy workload and moderate dermal exposure. On this supposition, exposure adjustments for unconventional shifts seems to be unnecessary unless the work schedule is extreme.

CONCLUSIONS

Unconventional work schedules increase the risk potential of adverse effects. But unconventional schedules, unless the exposures are extremely long, increase the risk potential less than twice (AF $\geq$0.5), thus keeping the range of increased risk within the range induced by physical stress of workload and dermal exposure. In the case of exposures under physical stress of workload, reduction of the exposure is not called for, because, it is believed, the safety factor incorporated in the permissible exposure limits protects the exposed worker against the increased uptake induced by the workload. It can be assumed, therefore, that there is no need for exposure adjustment for unconventional work schedules, except in extreme conditions, such as when working hours are more than doubled. In the case of extreme conditions, the exposure concentration should be reduced. The AF can be determined by using the half-life and the measure of the body burden (biological level or AUC) best related to the critical toxic endpoint. For agents with multiexponential elimination, it is critical to use the half-life that defines the uptake and elimination of the target organ (usually well perfused tissues characterized by the shortest half-life). Exact calculation of AFs is complex. In field conditions, AFs can be estimated using an appropriate equation from Table II. To calculate the toxicokinetic equivalent for unconventional shift, the exposure limit permissible for conventional work week is multiplied by the appropriate AF.

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