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TIMING OF SAMPLE COLLECTION FOR BIOLOGICAL MONITORING OF OCCUPATIONAL EXPOSURE

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Abstract—The timing of sample collections for the biological monitoring of occupational exposure profoundly affects the resulting data. Sampling time with respect to the day in the working week and the end of exposure is crucial for measurements of rapidly excreted indicators of exposure. Owing to the cumulation of slowly excreted exposure indicators, timing of sample collection with respect to the duration of employment is essential. The steady state is established within a week, if the exposure indicator is excreted rapidly (with a half-life shorter than 45 h), or within months or years, if it is excreted slowly. In this study, exposure indicators are characterized by the elimination half-life. A monocompartmental model is used to calculate the biological levels at steady state and the duration of occupational exposure needed to reach the apparent steady state. © 1997 British Occupational Hygiene Society. Published by Elsevier Science Ltd

In the biological monitoring of occupational exposure, the timing of specimen collection profoundly affects the resultant data. For exposure indicators with rapid elimination, the timing of sample collection in relation to the beginning and/or end of the exposure is crucial. Selection of the sampling day can be also critical because of the cumulative effect of previous exposure during the week. The sampling times of biological specimens for measurements of rapidly excreted metabolites, with elimination half-lives of a few hours, such as phenol, hippuric acid and mandelic acid, are properly included in the definition of the reference values for each of these exposure indicators (BEI, BAT). When the half-life is so short that the timing cannot be controlled in field conditions, biological monitoring is unsuitable. Such is the case with the monitoring of organic solvents in exhaled air collected during the first hours following the end of exposure, when the half-life is only a few minutes.

The rising of biological levels over months and years due to cumulation should be considered whenever biological specimens are intended for measurements of exposure indicators with a long half-life. For biological monitoring of some metals (with half-lives of years), a 'waiting period' is suggested (American Conference of Governmental Industrial Hygienists, 1991; Deutsche Forschungsgemeinschaft, 1995), but no general guidelines were found for sampling biological specimens in order to monitor exposure indicators with a long half-life.

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In this study, a monocompartmental toxicokinetic model was used to determine how long it takes to establish the apparent steady state during occupational exposure. The information is used to determine the minimum length of a worker's employment after which the reference values can be properly applied.

METHODS

The exposure indicators are characterized by the elimination half-life. The computations were performed in double precision, using an IBM personal computer.

Mathematical approaches

Single exposure. Biological levels at the end of exposure (A) and at the end of the resting post-exposure period (B) are described by the following exponential equations:

$$A = B_0 e^{-kx} + C(1 - e^{-kx}) \quad (1)$$

$$B = A e^{-ky} = B_0 e^{-k(x+y)} + C(e^{-ky} - e^{-k(x+y)}) \quad (2)$$

where x and y denote durations of the exposure and post-exposure resting periods, respectively; k is a rate constant related to the half-life ($k = \ln 2 / t_{1/2}$); B_0 denotes the residue from previous exposures (which, in this case, equals zero); and C is the biological level that will be reached if the given exposure lasts infinitely.

Occupational exposure. In a conventional work schedule, daily exposures lasting 8 h are followed by a resting period of 16 h, with the exception of the fifth post-exposure period which lasts 64 h. The biological levels at the ends of shifts, A_i , and of between-shift periods, B_i , are described by the following equations:

$$A_1 = B_0 e^{-8k} + C(1 - e^{-8k}) \quad B_1 = B_0 e^{-24k} + C(e^{-16k} - e^{-24k}) \quad (3)$$

$$A_2 = B_1 e^{-8k} + C(1 - e^{-8k}) \quad B_2 = B_1 e^{-24k} + C(e^{-16k} - e^{-24k}) \quad (4)$$

$$A_3 = B_2 e^{-8k} + C(1 - e^{-8k}) \quad B_3 = B_2 e^{-24k} + C(e^{-16k} - e^{-24k}) \quad (5)$$

$$A_4 = B_3 e^{-8k} + C(1 - e^{-8k}) \quad B_4 = B_3 e^{-24k} + C(e^{-16k} - e^{-24k}) \quad (6)$$

$$A_5 = B_4 e^{-8k} + C(1 - e^{-8k}) \quad B_5 = B_4 e^{-72k} + C(e^{-64k} - e^{-72k}) \quad (7)$$

The indexes denote the sequence of shifts during the work week (Fig. 1). In general terms:

$$A_i = B_{i-1} e^{-8k} + C(1 - e^{-8k}) \quad B_i = B_{i-1} e^{-24k} + C(e^{-16k} - e^{-24k}) \quad (8)$$

The exception is the calculation of B_5 , for which the exponent has to be modified in order to include the weekend period [Equation (7)].

The biological levels at the end of the shifts, and prior to the shifts, are obtained

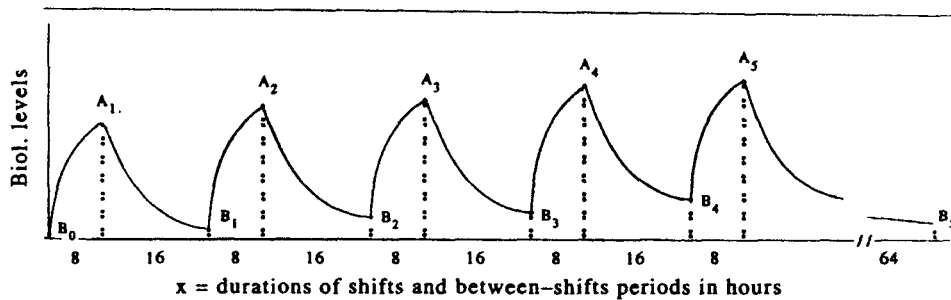


Fig. 1. The rise and decline of biological levels of an occupational exposure indicator over the working week. A indicates the biological levels at the end of the shift, B is the biological levels prior to the shift. For definitions, see Equations (3-8).

by consecutive substitution from Equations (3-6) into Equations (4-7). For example, the biological level at the end of the second day (that is, prior to the start of the third shift) is:

$$B_2 = B_0 e^{-48k} + C e^{-16k} (1 - e^{-8k} + e^{-24k} - e^{-32k}) \quad (9)$$

At the end of the week (prior to the first shift of the second week), the biological level is:

$$B_5 = B_0 e^{-168k} + C e^{-64k} (1 - e^{-8k} + e^{-24k} - e^{-32k} + e^{-48k} - e^{-56k} + e^{-72k} - e^{-80k} + e^{-96k} - e^{-104k}) \quad (10)$$

B_5 , which represents residues from previous exposures, rises over the weeks, until the steady state is reached.

At steady state, the biological levels at the beginning and the end of the week, are the same ($B_0 = B_5 = B_{0ss}$), and Equation (10) is written as:

$$B_{0ss} = \frac{C e^{-64k}}{1 - e^{-168k}} (1 - e^{-8k} + e^{-24k} - e^{-32k} + e^{-48k} - e^{-56k} + e^{-72k} - e^{-80k} + e^{-96k} - e^{-104k}) \quad (11)$$

Biological levels at steady state are then calculated by substituting B_{0ss} from Equation (11) for B_0 in Equation (3), and proceeding in sequence to Equation (7).

The biological level at the end of the fifth shift (which is the highest biological level in the week) is:

$$A_{5ss} = \frac{B_{0ss}}{e^{-64k}} \quad (12)$$

The number of work weeks needed to reach steady state. Since the rise and decline of biological levels are described by exponential functions, the steady state is theoretically reached at infinity. In practice, the apparent steady state is considered to be established when the biological levels differ very little from the steady state value.

To investigate the establishment of the steady state of exposure indicators with different half-lives, the computation of weekly cycles begins by substituting zero for B_0 in Equation (3). In succeeding cycles, B_5 from the immediately preceding cycle is substituted for B_0 . The computations are repeated until the difference between B_0 [Equation (10)] and B_{0ss} [Equation (11)] is acceptable.

The biological levels at steady state, and the number of weeks needed to reach the apparent steady state, were computed for exposure indicators with half-lives between 1 h and 2 years. The computations were done for biological levels equal to the following percentages of the steady state levels: 99.99, 99.9, 99, 90, 75 and 50% (further referred to as 'apparent steady state').

RESULTS

The number of working weeks (length of worker's employment with the same exposure) needed to reach a selected percentage of the steady state level is shown in Fig. 2. The relation between the half-life and the number of weeks needed to reach the apparent steady state is described by a logarithmic function:

$$\log(w) = a \log(t_{1/2}) - q \quad (13)$$

where w denotes the number of weeks of the worker's employment, with exposure, needed to reach the apparent steady state, a is a slope which is equal to 1, and q is a constant dependent on the definition of the apparent steady state (Table 1). Half-life $t_{1/2}$ is given in hours. The number of weeks required to reach the steady state is independent of the exposure concentration as long as the concentration is in the range of linear kinetics. Permissible occupational exposures usually meet this requirement.

The third column in Table 1 indicates the longest half-lives which allow the reaching of the apparent steady state in the second working week. It is calculated as an antilogarithm of q in Equation (13) (for $w=1$, and $a=1$, $\log t_{1/2}=q$), and pictured as x-intercepts in Fig. 2. For the purpose of biological monitoring, biological levels equal to 90% of the steady state level are acceptable. Thus exposure indicators with a half-life shorter than 45 h reach the apparent steady state during the second week of exposure. Exposure indicators with a longer half-life require months or years of occupational exposure to reach the apparent steady state.

DISCUSSION

It is known that, for rapidly excreted indicators of occupational exposure, the timing of specimen collection with respect to the beginning and the end of exposure is crucial. This study shows that the length of employment significantly affects biological levels of slowly excreted exposure indicators. Biological levels of exposure indicators with long half-lives rise over weeks, due to cumulation. The rising ceases at the steady state, when the weekly cycle of biological levels repeats itself. Because of the large variability of biological levels induced by environmental factors and by the physiological parameters of the exposed workers, sampling for biological monitoring is acceptable when the biological level reaches 90% of the steady state

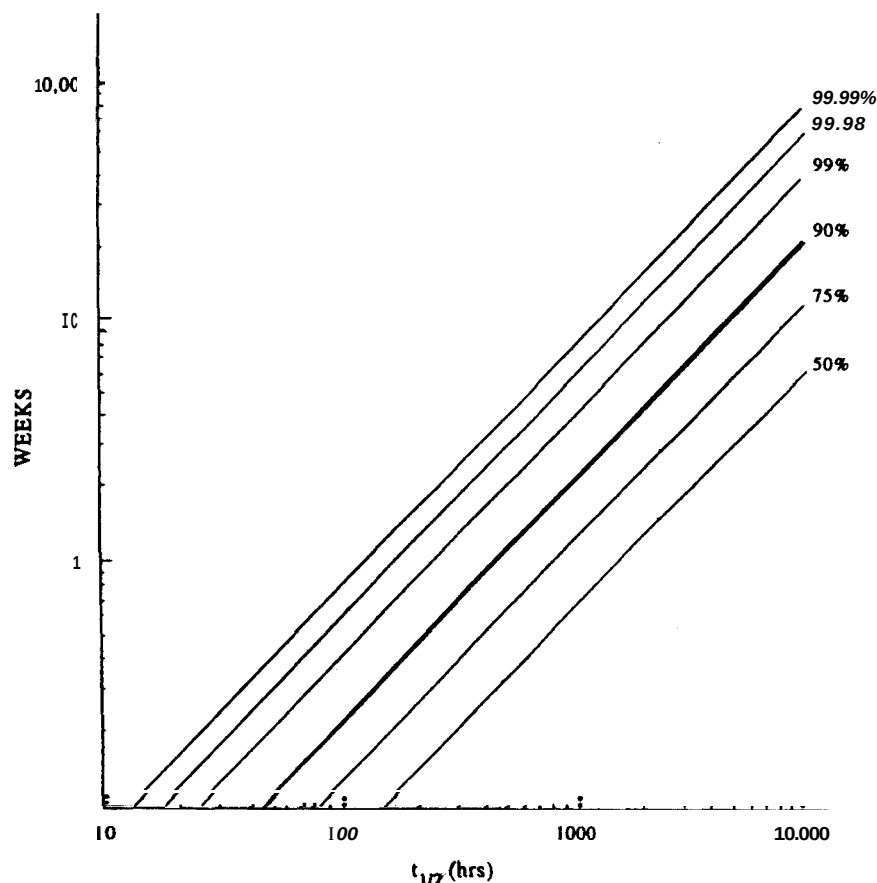


Fig. 2. Dependence of the number of working Weeks required to reach apparent steady state on the half-lives of occupational exposure indicators. The percentages relate the biological levels at apparent steady state to steady state levels **calculated** using Equation (12). The calculation describes conventional **work** cycles of five 8 h shifts per week. The intercepts on the abscissa indicate the longest half-lives which allow the apparent steady state to be reached during the first working week.

level. Since the reference values for biological monitoring (such as BEI and BAT) are meant for steady state conditions, biological specimens should be collected after a 'waiting period'. The waiting period for exposure indicators with different half-lives can be estimated from the bold line in Fig. 2 (indicated by 90%), or calculated using Equation (13). Fig. 2 can also be used to estimate what fraction of the steady state value represents the measurement taken after a known length of employment.

For practical purposes, it is satisfactory if the reference values are compared with measurements in samples collected as follows:

- (a) $t_{1/2} < 45$ h: sampling after 1 week of exposure. Day in the working week and timing in relation to the beginning and the end of exposure are critical.
- (b) $t_{1/2} < 9$ days: sampling after 1 month of employment. At steady state, timing with respect to the shift is critical only if $t_{1/2} < 4$ days.

Table 1. Constants q for Equation (13)

Levels*	q	$t_{1/2}^\dagger$
99.99%	1.110	13 h
99.9%	1.228	17h
99.0%	1.401	25 h
90.0%	1.665	45 h
75.0%	1.921	83 h
50.0%	2.165	166 h

*Biological levels at apparent steady state expressed as percentage of biological level at real steady state.†Longest half-lives which allow reaching of apparent steady state during the first work week. They equal antilogarithms of q . (See x-intercepts in Fig. 2.)

- (c) $t_{1/2} < 3$ months: sampling after 1 year of employment. Timing with respect to the shift and working week is unimportant.
- (d) $t_{1/2} > 3$ months: sampling should be repeated each 6 months. A rise in the biological level and possible exceeding of the reference value should be observed.

For example, the elimination of cadmium in urine ($t_{1/2} = 12$ h, 2.7 days, and 10 years), is triphasic. The shortest half-lives, which control the rapid rise of biological levels at the beginning of employment, indicate that sampling after 1 week of employment is appropriate. The long half-lives, however, indicate that regular yearly control is necessary. Fig. 2 indicates that measurements taken after around 30 weeks of employment represent about 50% of the lifetime employment level, and that measurements taken after 1 year of employment represent about 75% of the lifetime employment level. Half-lives of lead in blood ($t_{1/2} = 1.3$ month, 6 months, and 40 years) indicate that the steady state would be reached after 70 years of employment. This means that the lead levels in blood rise over the whole working life, making periodical checkups advisable. However, half-lives of indicators of exposure to organic solvents are shorter than 3 days. This means that the apparent steady state is reached within a month of employment, but sampling time with respect to the week day is critical.

The recommended sampling times of biological specimens based on the half-life of the exposure indicators are shown in the last column of Table 2.

Conclusions

Special attention should be given to the sampling time of biological specimens for measurements of exposure indicators. For indicators with a short half-life, the timing is crucial with respect to the day in the working week and to the beginning and end of the shift in which exposure occurs. Recommended sampling times for reference values should be followed strictly. For agents with a long half-life, the timing of 'sampling is crucial with respect to the duration of employment (not with respect to the work shift). A regular yearly check-up is indicated. The reference values (BEI, BAT) for slowly eliminated exposure indicators indicate that timing is 'not critical' (BEI), is 'discretionary' (BEI), or that sampling 'after several shifts' (BAT), is recommended. It would be more appropriate if the reference values

Table 2. Half-lives of Exposure Indicators (BEIs)

	Notation	Half-lives of BEIs			Recommend.
		Hours	Days	Years	
ACETONE					
Acetone, ur.	ES	3.5			ES a
ANILINE					
p-aminophenol	ES	3, 10			ES, EW a
ARSENIC					
Inorganic As, ur.	EW		1, 3.5, 8		EW b
BENZENE					
phenol. ur.	ES	6	1.2		ES, EW b
benzene, air	PS	0.4, 2.5	1.25		PS, EW b
CADMIUM					
Cd, ur.	NC	12	2.1	10-30	d
Cd, bl.	NC			.3, 10	d
CARBON DISULFIDE					
TTCA, ur.	ES	2	**		ES, EW a
CARBON MONOXIDE					
CO-Hb, bl.	ES	5			ES, EW a
CO, air	ES	5			ES, EW a
CHLOROBENZENE					
4-chlorocatechol, ur.	ES	2.2	.72		ES, EW a
p-chlorophenol, ur.	ES	3	.5		ES, EW a
CHROMIUM (VI)					
Cr, ur.	ES, EW	7	15-30	3-5	d
COBALT					
Co, ur.	ES, EW		42		c
Co, bl.	ES, EW	12	2.7, 59		c
N,N-DIMETHYLACETAMIDE					
N-Methylacetamide, ur.	ES, EW		.67		ES, EW a
N,N-DIMETHYLFORMAMIDE					
N-methylformamide, ur.	ES	3, 7			ES, EW a
2-ETHOXYETHANOL					
2-ethoxyacetic ac., ur.	ES, EW		1.9		ES, EW b
ETHYLBENZENE					
Mandelic acid, ur.	ES, EW	5	1		ES, EW a
FLUORIDES					
FL, ur.	ES	4-7			ES, EW a
FURFURAL					
furoic acid, ur.	ES	2			ES a
n-HEXANE					
2,5-hexanedione, ur.	ES	14			ES, EW a
LEAD					
Pb, bl.	NC		40	.5, 40	d
MERCURY					
inorg. Hg, ur.	PS		40		c
inorg. Hg, bl	ES, EW		10, 28	.5	d
METHANOL					
methanol, ur.	ES	2			ES a
METHYLCHLOROFORM					
methylchloroform. air	PS, EW	1,5	1.3		PS, EW a
TCAA, ur.	EW		3		ES, EW b
TCE, ur.	ES, EW	11			ES, EW a
TCE, bl.	ES, EW	11			ES, EW a
METHYL ETHYL KETONE					
MEK, ur.	ES	.5, 1.35			ES a
METHYL ISOBUTYL KETONE					
MIBK, ur.	ES	.7, 7			ES, EW a
NITROBENZENE					
p-nitrophenol, ur.	ES, EW	8			ES, EW a

Table 2—continued

	Notation	Half-lives of BEIs			Recommend.
		Hours	Days	Years	
PARATHION					
p-nitrophenol, ur.	ES	8			ES, EW a
PENTACHLOROPHENOL					
PCP, ur.	PS, EW		1.2	.2	c
PCP, pl.	ES		1.2, > 30		c
PERCHLOROETHYLENE					
perchloroethylene, air	PS, EW	28, 4.3	3.1		PS, EW b
perchloroethylene, bl.	PS, EW	.25, 4	4		PS, EW b
TCAA, ur.	EW		3.3		ES, EW b
PHENOL					
phenol, ur.	ES	3.5			ES a
STYRENE					
mandelic acid, ur.	ES	3.5	1.4		ES, EW a
	PS				PS, EW a
phenylglyoxylic ac., ur.	ES	8			ES, EW a
	PS				PS, EW a
styrene, bl.	ES	.6, 13			ES, EW a
	PS				PS, EW a
TOLUENE					
hippuric acid, ur.	ES	2			ES a
toluene, bl.	ES	.5, 3.1	3.2		ES, EW b
TRICHLOROETHYLENE					
TCAA, ur.	EW		3		ES, EW b
TCAA + TCE, ur.	ES, EW				ES, EW b
TCE, bl.	ES, EW	12			ES, EW a
VANADIUM PENTOXIDE					
V, ur.	ES, EW		.8		ES, EW a
XYLENES					
methylhippuric ac., ur.	ES	3.6	1.25		ES, EW a

Notation indicates sampling time for BEIs: ES = end-of-shift; PS = prior-to shift; EW = end-of-week; NC = not critical or discretionary.

ur. = urine sample; bl. = blood sample; air = exhaled air sample.

Recommendation is based on the half-life analysis in this paper. a-d, which relates to cumulation over the long-term employment, are explained in text. EW is based on the half-life of the BEI as shown in the Appendix. Half-lives as cited in BEI documentation (American Conference of Governmental Industrial Hygienists, 1991).

* There are indications of cumulation of 2-thiothiazolodine-4-carboxylic acid. The half-life of the slow phase, however, is not determined. EW notation is used as a precaution.

defined the 'waiting period', and discouraged sampling shortly after a worker had returned to work from a vacation or other long absence.

REFERENCES

- American Conference of Governmental Industrial Hygienists (1991) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, Sixth Edition. Cincinnati, OH.
- Deutsche Forschungsgemeinschaft: List of MAK and BAT Values 1995, Report No. 31. VCH Verlagsgesellschaft, Weinheim.

APPENDIX

ES indicates that sampling at the end of the shift is required for agents with a half-life shorter than 4 days. This criterion is based on the assumption that the

biological level at steady state prior to the shift equals 90% of the level at the end of the shift. The half-life meeting this criterion was derived by consecutive substitution from Equations (3-6) into Equations (4-7) until $A_i/B_i = 0.9$.

EW indicates that sampling at the end of the working week is required for agents with a half-life between 4 and 217 h (about 9 days). This criterion was derived as follows:

- (a) It is assumed that, in order to prevent the cumulation over the week, the residue 16 hours after the shift should not exceed 5% of the value at the end of the shift. Thus

$$0.05C = Ce^{-16k} \quad \text{i.e. } e^{-16k} = 0.05$$

Thus

$$k = \frac{\ln 0.05}{-16} = 0.1872t_{1/2} = 3.7h$$

- (b) It is assumed that the fluctuation during the working day becomes insignificant if the difference between the end-of-shift level and prior-to-shift level is less than $\pm 5\%$ of the end-of-shift level. Thus

$$0.95(1 - e^{-8k}) = (1 - e^{-8k})e^{-16k} \quad \text{i.e. } e^{-16k} = 0.95$$

Thus

$$k = \frac{\ln 0.95}{-16} = 0.003206t_{1/2} = 216.2h$$