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Effects of Time-Variant Exposure on Toxic Substance Response

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Sources of time-variant exposure to toxic substances are identified and examined for their effects on the estimation of response. It is shown that only time-averaged target tissue concentrations are required to obtain rigorous risk estimates from the one-hit and multihit models. In contrast, detailed concentration histories need to be retained throughout analyses involving two-event models with intermediate-stage clonal growth advantage (clonal two-stage) and multistage models. Cumulative incidence ratios, based on the exact to time-averaged treatment of concentration time dependencies, are evaluated for substances whose toxic responses exhibit moderate (arsenic) and strong (ethylene dibromide) dependence on time of actual exposure. These ratios reveal that time-averaged dose approximations may lead to several orders of magnitude error in both the multistage and clonal two-stage models if exposure periods are short, and that 3.4-fold (arsenic) and 8-fold (ethylene dibromide) errors still exist even when an actual two-thirds lifetime exposure is averaged over a full lifetime. Finally, the effects of time-variant exposure on risk estimation due to migration and birth-death in an epidemiological setting are examined. A residence time distribution calculation shows that, if these effects are ignored for a population orally exposed to arsenic and characterized by an out-migration rate in excess of 5%/yr, response errors will exceed an order of magnitude.

Introduction

The probability that an individual will exhibit a toxic end point following exposure to a toxic substance is usually estimated either from the responses of experimental animals or from humans exposed to the substance in an epidemiological setting. For ease of computation, these animals or humans are often assumed to receive a constant dose rate over the exposure period. However, in virtually all epidemiological settings and in many animal experiments, this condition is not satisfied. As a result, time-variant dose is often time averaged to provide the constant dose rate needed for simple computation. This procedure may or may not lead to substantial error in estimating an individual's probability of response and, hence, it requires examination.

Previous investigators have addressed the role of time-dependent dosage in specific response models. Whittemore and Keller (*1*) presented general expressions for incidence rates derived from the multistage model when dosage was time-dependent, as well as particular solutions when a constant dose rate was administered from birth to an arbitrary time. They applied these step solutions to the analysis of tumor incidence data from mice skin-painted with benzpyrene (*2*). Day and Brown (*3*) provided additional multistage incidence expressions for step-type dosage schedules when exposure occurred late in life. Whittemore and Keller (*1*) also presented a formal solution for including time-dependent dosing in the modified multistage models of Armitage and Doll (*4*) and Fisher (*5*), in which intermediate stage cells were allowed to grow more rapidly than normal cells, but they did not exercise these models over a range of specific time-dependent schedules.

More recently, Crump and Howe (*6*) developed solutions for cumulative incidence predicted by the multistage model when dosage was time-dependent. Their method was general in the sense that it held for dosage patterns describable as a superposition of square wave forms. Since there was no restriction on the number of square waves superimposed, theoretically, any time-dependent dosage function could be described to as high a degree of approximation as desired.

This report complements earlier work by discussing the various sources of time-variant exposure, identifying models that yield rigorous response estimates from time-averaged doses, further identifying error patterns in other model estimates introduced by the use averaged-dose approximations, and assessing the magnitude of migration-related effects in epidemiological response. The dose-response models considered are the one-hit, multihit, multistage, Weibull, and clonal two-stage [modified multistage of Armitage and Doll (*4*)] models. The principal toxic end point under consideration will be cancer, but a few comments will also be made about reproductive toxicity.

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Sources of Time-Variant Exposure

The response induced by a toxic agent ultimately depends on the exposure to this substance or one of its metabolites at the target tissue. Time dependence in this exposure may thus arise either from nonconstant dosing at the level of the whole organism or from pharmacokinetic transients at the tissue level resulting from toxic substance distribution and metabolism. A common source of exposure variation at the whole organism level is a time-dependent administration schedule in animal experiments. This often results from alterations imposed on an initial schedule during the course of an experiment, as, for example, when excessive mortality occurs in the animal population and the dose level must be reduced. Other common sources of exposure time dependence at the organism level include variable release patterns of toxic agents in environmental exposure and variable exposure in an epidemiological setting due to people migrating into and out of a geographical region.

Pharmacokinetic events may occur over a wide range of time scales and are thus a source of time-dependent exposure, yet the longest of these scales is often too short to warrant formal inclusion of pharmacokinetic transients in dose-response analysis, particularly in carcinogenesis studies. Hydrophilic substances are typically cleared quite rapidly by the body with plasma half-times on the order of a few hours. Hydrophobic materials may be characterized by larger half-times due to their high retention in fatty tissues. However, even an extremely fat-soluble species may be characterized by a half-life that is long by pharmacokinetic standards, but is still short compared to the length of continuous administration often employed in cancer animal experiments, periods of 1 year or more. For example, the late plasma half-life of 2,4,5,2′,4′,5′-hexachlorobiphenyl in the dog is 19 days (*7*), a value far larger than encountered with most hydrophilic substances but much less than a year. Hence, under conditions of nearly continuous administration (e.g. daily gavage), many if not most substances will reach steady-state tissue distributions, and only pharmacokinetic steady-state concentrations need be employed in dose-response calculations.

On the other hand, situations do exist in which nonsteady-state pharmacokinetics play a significant role in determining time-dependent exposure. For example, in noncanine species such as the mouse, rat, and monkey, 2,4,5,2′,4′,5′-hexachlorobiphenyl is characterized by extremely long time constants (*7*). The compound is metabolized very slowly in these species and this, coupled with its high fat solubility, allows it to continually accumulate in the body over periods of administration comparable to animal lifetimes. Thus, the pharmacokinetics of this chemical species remain time-dependent over most of the course of an animal experiment.

Another situation in which time-dependent pharmacokinetics may play a major role is in the area of reproductive toxicity testing. In this case, reproduction toxicities such as the occurence of malformations are assessed after relatively short periods of toxic agent administration, for example over days 6 to 15 of gestation in the mouse. For many agents, this short administration period brings the time scale for induction of reproductive lesions much closer to the scale of pharmacokinetic transients and raises the possibility that their description must be retained throughout any subsequent dose-response analysis.

Concentration Time-Dependency in Dose-Response Models

The detailed accounting of the dose dynamics arising from the sources of time-variance just presented is highly dependent upon the response model chosen to represent toxic response. We will show that the one-hit and multihit models allow a rigorous estimation of risk (incidence or cumulative incidence of response) from only the time-averaged target tissue concentration, while the multistage and clonal two-stage models generally require that detailed time-dependency be retained throughout risk estimation. Numerical estimates of the magnitude of these time-dependent effects will be presented for carcinogenic end points attributed to compounds whose response exhibits an intermediate (arsenic) and strong (ethylene dibromide) dependence on exposure time.

One-Hit Model

In this model, the probability $\lambda(t)$ for irreversible transition of a cell from a normal to malignant state is taken as proportional to the target tissue concentration $c(t)$, i.e., $\lambda(t) = a + b\,c(t)$. From Whittemore and Keller (*1*), the differential equation for the probability of a cell being normal at time t is

$$dp_0(t)/dt = -\lambda(t)p_0(t) \qquad p_0(0) = 1 \qquad [1]$$

Solving this equation for p_0, and noting that $p_1 = 1 - p_0$ is the probability of this cell having undergone the toxic transition, one obtains

$$p_1(t) = 1 - \exp(-at - b\int_0^t c(t)dt)$$

Because the time-averaged dose $<c>$ is defined as the integral in this expression divided by t,

$$p_1(t) = 1 - \exp(-at - b < c > t) \qquad [2]$$

Thus, rigorous toxicity estimates made from the one-hit model only require knowledge of the averaged target tissue dose.

Multihit Model

This model (*8*) assumes that k irreversible alterations, each with an identical transition probability $\lambda(t)$, must occur in an individual before a toxic state is reached. Differential equations for the probability of observing

a normal individual (p_0) and individuals with n-hits (p_n) are of the form of Equation 1 and

$$dp_n(t)/dt = \lambda(t)p_{n-1}(t) - \lambda(t)p_n(t) \qquad p_n(0) = 0$$

Recursive solution of these equations allows one to write an expression for the probability P of observing a toxic response consisting of k or more hits, i.e.,

$$P = \sum_{n=k}^{\infty} p_n = \frac{1}{\Gamma(k)} \int_0^{\Lambda(t)} x^{k-1} e^{-x} dx$$

where

$$\Lambda(t) = \int_0^t \lambda(t)dt = at + b < c > t \qquad [3]$$

Because P depends only on the averaged target tissue concentration through the $\Lambda(t)$ limit, the multihit model, like the one-hit, does not depend on the detailed time pattern of target tissue dosing.

Multistage Model

This model (*9*) assumes that k irreversible hits must occur in the order $0,1,\ldots,k-1$ with the transition probability for each hit being $\lambda_i(t) = a_i + b_i\, c(t)$. No cells except the final stage cells are assumed to undergo growth. The general differential equations for this model have been presented in Whittemore and Keller (*1*). Ignoring the time for growth of tumor to detectable size, the cumulative incidence of tumors P derived for this model is

$$P = 1 - \exp\left[-N \int_0^t \lambda_{i-1}(t_{i-1}) \ldots \int_0^{t_2} \lambda_1(t_1) \int_0^{t_1} \lambda_0(t_0) dt_0 dt_1 \ldots dt_{i-1} \right] \qquad [4]$$

where N is the number of cells in a target organ. This multiple integral results from the model's requirement that the hits occur in a particular sequence, and its form generally does not allow the cumulative incidence of tumors to be expressed in terms of $<c>$. Thus, detailed time-dependence of the target tissue concentration must be taken into account.

Whittemore and Keller (*1*) and Day and Brown (*3*) evaluated P for special cases of step function exposure. Crump and Howe (*6*) evaluated it for the more general dose pattern of superimposed square waves, provided that the toxic agent acts at no more than two stages. Their method may be easily extended to other dosage patterns such as the exponential decay functions encountered in linear pharmacokinetics. Solutions involve summations over incomplete gamma functions.

To demonstrate the magnitude of time-dependent concentration effects relative to their treatment as time-averaged quantities, we evaluate the ratio R of the lifetime cumulative incidence, computed for various time-dependent tissue concentrations, to the corresponding averaged concentration value. Thus,

$$R = \frac{P[c(t)]}{P[<c>]} \qquad [5]$$

The farther R is from unity, the poorer the dose-averaged concentration approach. R is identically 1 for the one-hit and multihit models, as tabulated in Table 1.

We have computed multistage R values appropriate to skin cancer induction by oral exposure to arsenic (*10*) [presumably present as arsenate/arsenite in drinking water (*11*)] and to induction of carcinoma of the rat forestomach by ethylene dibromide (*12*), and tabulated the results in Tables 1 and 2. Previous work has shown that arsenical skin cancer prevalence exhibits a 3.88 ± 0.33 Weibull power dependence on exposure time beginning at birth, a figure insignificantly different from 4 (*13,14*). Ethylene dibromide, on the other hand, exhibits a stronger dependence on this exposure time, the corresponding power being 6 (*6*). Hence, R values for these

Table 1. Ratio of actual to dose-averaged lifetime-response for various models.[a]

Model	Exposure initiation time[b] Early	Late
One-hit	1	1
Multihit	1	1
Multistage		
Arsenic[c]	2.4	1/27
Ethylene dibromide[d]	3.0	1/250
Clonal two-stage[e]		
Dose, ppm:		
0	2.5	1/18
0.15	2.4	1/16
1.20	1.8	1/11
5.00	1.04	1/5.8
20.0	1	1/1.4
Infinity	1	1

[a] Fixed exposure interval of one-third lifetime.
[b] Early, initiation time at birth; late, initiation time two-thirds of way through life.
[c] Arsenic multistage assumes four stages, the first being dose related.
[d] Ethylene dibromide assumes six stages, the first being dose related.
[e] This model is applied to arsenic exposure, assuming that both stages are dose related.

Table 2. Ratio of actual to dose-averaged response: Effect of exposure interval.[a]

Length of exposure	Exposure initiation time[b]	Ratio (R) EDB[c]	As
Bolus[d]	0.0	6	—
	0.57	1/11	—
	0.86	1/2500	—
One-third lifetime	0.0	3	2.4
	0.67	1/250	1/27
Two-thirds lifetime	0.0	1.5	1.5
	0.33	1/8	1/3.4

[a] Multistage models.
[b] Units of fractional lifetime.
[c] Ethylene dibromide.
[d] From (*6*).

chemical species provide examples of moderate and strong dependence of response on time-dependent exposure effects.

The cumulative incidences comprising R, $P[c(t)]$, and $P[<c>]$ were computed for arsenic and ethylene dibromide from Equation 4 when only the first stage of the four or six involved is affected by toxic agent (i.e., only $b_1 \neq 0$). Earlier work showed that the assumption of a single affected stage led to good fits of experimental response data (*6,13*). The multistage R values in Tables 1 and 2 were computed for two types of dosage administration patterns. For simplicity, tissue pharmacokinetics were assumed to always be at steady state with the current rate of administration. Table 1 presents values for a fixed exposure period of one-third lifetime, with this period occurring either during the first third of life (early exposure) or the last third (late exposure). Both $P[c(t)]$ and $P[<c>]$ were evaluated from equations of Crump and Howe (*6*) where $c(t)$ was the square wave

$$c(t) = \begin{cases} c_0 & s_1 \leq t < s_2 \\ 0 & \text{otherwise} \end{cases} \qquad [6]$$

and

$$P[c(t)] = 1 - \exp[-q_0 t^k - q_1 Z_{1k}(t)] \qquad [7]$$

$$Z_{1k} = c_0 \begin{cases} 0 & t < s_1 \\ (t - s_1)^k & s_1 \leq t < s_2 \\ (t - s_1)^k - (t - s_2)^k & s_2 \leq t \end{cases}$$

[Multistage ratios similar to our R values were computed in (*6*) for ethylene dibromide but, generally, reference probabilities other than $P[<c>]$ were reported.]

The multistage results for arsenic show that inclusion of dose time-dependence leads to a 2.4-fold higher estimate of cumulative incidence during early exposure than time-averaged doses, and to a 27-fold lower estimate during late exposure. By contrast, the time-dependent cumulative incidence of ethylene dibromide estimated for late exposure is about 10-fold again lower, i.e., 250-fold lower than the averaged-dose result. This is a straightforward reflection of ethylene dibromide's greater dependence of response on exposure time. As observed by previous investigators in related analyses, the much smaller R values for late exposure are a consequence of assuming that only the first stage is affected by carcinogen; the time-averaged dose approach improperly provides for large dosing early in life, allowing many cells to undergo early first-stage transition and to have much more time to reach the final transformation stage than would be allowed by the actual dosage pattern.

Table 1 presents examples of the magnitude of time-dependent dosage effects for a fixed exposure period (one-third of a lifetime). These multistage results are expanded in Table 2 to examine the effects of varying the exposure period. As expected, the late bolus results for ethylene dibromide (*6*) show the most extreme divergence of time-dependent and time-averaged doses, nearly three orders of magnitude when the bolus is given 0.86 through a lifetime. The other R values in Table 2 demonstrate that this divergence decreases as the exposure time is lengthened, but that over a two-order of magnitude difference still remains for late one-third lifetime exposure and nearly an order of magnitude for two-thirds of a lifetime exposure. For the arsenic example, the effects are less dramatic due to this agent's weaker dependence of response on exposure time, but they do not drop to less than an order of magnitude until (late) exposure lengthens to two-thirds of a lifetime or more. Hence, time-dependent concentration effects may be extremely important in estimating multistage responses, even when exposure periods are large fractions of a lifetime.

Clonal Two-Stage Model

This modified multistage model (*4*) assumes that toxic response occurs after two irreversible stages and that cells of intermediate stage may proliferate to advantage over normal cells. This model is the deterministic limit of the Moolgavkar and Venzon (*15*) two-event model when the number of normal susceptible cells remains constant (*16*). We include this model in our survey of time-dependent concentration effects because it is more biological than pure multistage models due to its allowance of differential growth, and because it may eventually serve as a starting point for introduction of activated oncogene effects. Furthermore, as we will apply it, both normal and intermediate cells will be assumed sensitive to the action of toxic agent, rendering the cumulative incidence ratio R a function of tissue dose and providing us with an extra dimension in which to investigate time-dependent effects.

The mean equations for this model are

$$dN_0/dt \sim 0$$

$$dN_1/dt = \lambda_1 N_0 + kN_1$$

$$dN_2/dt = \lambda_2 N_1$$

where N_0 is the constant number of normal susceptible cells, N_1 is the number of intermediate cells with growth rate constant k, N_2 is the number of transformed clones, and $\lambda_i = a_i + b_i c(t)$. These equations may be integrated to yield the probability, $p_2(t)$, that an individual cell will become a cancerous clone at time t

$$p_2(t) = \frac{N_2(t)}{N_0} = \int_0^t \lambda_2(t_2) e^{kt_2} \int_0^{t_2} \lambda_1(t_1) e^{-kt_1} dt_1 dt_2 \qquad [8]$$

Alternatively, the probability P of there being at least one tumorous clone in an individual at time t (cumulative incidence) may be calculated as

$$P(t) = 1 - \exp(-N_0 p_2) \qquad [9]$$

The Equation 8 result contrasts with Equation 4 because of the additional exponential growth terms.

For constant dosing c_0 over the entire observation interval $[0,t]$,

$$P = 1 - \exp[(q_0 + q_1c_0 + q_2c_0^2)(1 + kt - e^{kt})] \quad [10]$$

where $q_0 = N_0a_1a_2 / k^2$, $q_1 = (a_1b_2 + a_2b_1) N_0 / k^2$, and $q_2 = N_0b_1b_2 / k^2$.

For time-dependent tissue dosing, we again consider the square wave tissue dosing pattern where $c(t) = c_0$ over the interval $s_1 \leq t < s_2$ and is zero otherwise (Eq. 6). Integration of Equation 8 for this pattern and substitution into Equation 9 yields an expression, $P[c(t)]$, for cumulative incidence as a function of a time-dependent concentration:

$$P[c(t)] = 1 - \exp[-N_0(I_1 + I_2 + I_3 + I_4)]$$

$$I_1 = (a_1a_2/k)[(e^{kt} - 1)/k - t]$$

$$I_2 = (b_2a_1c_0/k)\begin{cases}0\\(e^{kt} - e^{ks_1})/k - t - s_1\\(e^{ks_2} - e^{ks_1})/k - s_2 + s_1\end{cases}$$

$$I_3 = (a_2b_1c_0/k)\begin{cases}0\\[e^{k(t-s_1)} - 1]/k - t + s_1\\e^{-k(s_1+s_2-t)}[e^{ks_2} - e^{ks_1}]/k + s_1 - s_2\end{cases}$$

$$I_4 = (b_1b_2c_0^2/k)\begin{cases}0\\e^{-ks_1}(e^{kt} - e^{ks_1})k + s_1 - t\\e^{-ks_1}(e^{ks_2} - e^{ks_1})/k + s_1 - s_2\end{cases} \quad [11]$$

and the entries in brackets correspond to $t < s_1$, $s_1 \leq t < s_2$, and $t \geq s_2$, respectively.

We again demonstrate the magnitude of the time-dependent concentration effect on cumulative incidence by forming the ratio of $P[c(t)]$ to its corresponding time-averaged value, i.e., R of Equation 5. We evaluate R for arsenical skin cancer and for the same early [0,0.33] and late [0.67,1] one-third lifetime exposure periods used before with the multistage model.

The results are shown in Table 1 for six administered dose levels, since R remains a function of c_0 when two or more stages are carcinogen sensitive, as assumed in this model. Parameter values were obtained by fitting Equation 10 to the Tseng et al. data (*10*) ($q_0 = 0$, $q_1 = 0.0013$ ppm^{-1}, $q_2 = 0.0012$ ppm^{-2}, $k = 0.071$ yr^{-1}). Because $q_0 \propto a_1a_2$ was zero, but $q_1 \propto a_1b_2 + a_2b_1$ was not, either a_1 or a_2 (but not both) was zero. The Tseng et al. data could not discriminate between these possibilities and hence we considered both possibilities. The clonal two-stage entries in Table 1 are for the case $a_1 = 0$. The entries in the early and late columns switch for the case $a_2 = 0$.

The arsenic data of Table 1 show this model to be about as maximally sensitive to time-dependent concentration effects as the multistage. For the data of Table 1 ($a_1 = 0$), the greatest divergence between time-dependent and time-averaged response calculations occurs when the dose approaches zero and when exposure is late, the time-averaged response being 18-fold that of the true response. This compares to 27-fold for the pure multistage. (The same comparison holds when $a_2 = 0$ except that the greatest divergence occurs for early exposure.) The data also show that as the dose level increases, the time-averaged response becomes a better estimate, although it is still an order of magnitude in error (11-fold) at the highest epidemiologic dose level (1.2 ppm) reported by Tseng et al. (*10*). The R limit of unity occurs at large doses for both early and late exposures because these doses strongly affect both stages of arsenic transformation and drive the responses comprising both numerator and denominator of R to 1, regardless of the exposure pattern.

Time-Dependent Exposure Due to Migration and Birth-Death: Effect on Toxic Response Estimation

A special case of time-dependent dosage in the epidemiological setting involves the determination of exposure periods by migration and birth-death patterns of the exposed population. Because this is such a common circumstance in analyzing epidemiological data or in estimating environmental risk, we next assess the magnitude of effect that a typical human migration pattern has on estimation of toxic response.

In essence, estimating the response of a human population to a toxic agent involves summing over the responses of each group of people who have been exposed for the same length of time. Thus, if the residence time distribution for this population can be ascertained, an estimate of population toxic response may be made by convolving the residence distribution with the probability of response for a particular residence time. We therefore derive a residence time distribution for a simple population balance model, couple it to the multistage dose-response model, and examine predicted population toxic response as a function of migration rate. Oral arsenic exposure will again serve as a numerical example. We see that for large migration rates and intermediate exposure time sensitivities, neglect of migration and birth-death effects typically leads to an order of magnitude response error.

Population Balance Model

To keep the analysis simple, assume that the exposed region is a small geographic area in which people are exposed to toxic agent at a constant level c_0. At any time, this region is characterized by a residence time density function, $n(t,t')$, where t is chronological time beginning from the time that toxic agent emission started, t' is an individual's residence time during this period of emission ($t' < t,t$), and $n(t')$ is the number of people at time t who have lived in the area for a length of time between t' and $t' + dt'$. People who have just moved into the area or were just born there will have $t' = 0$, whereas others may have been there since emission began and will have $t' = t$.

If we assume that within the exposed population: (a)

the rate of in-migration is independent of the local population density (zeroth order in-migration rate); (b) the rate of out-migration is proportional to the local population density (first order out-migration); and (c) birth-death rates are first-order processes uncorrelated with either chronological or residence times (age-residence time correlation is ignored for this order of magnitude assessment), then a simple population balance model may be written as

$$\frac{\partial n(t,t')}{\partial t} = -\frac{\partial n(t,t')}{\partial t'} - (\lambda + \Delta)n(t,t') \qquad [12]$$

subject to the boundary conditions that

$$n(t,0) = \beta + \gamma\int_0^t n(t,t')dt' = \beta + \gamma N(t) \qquad [13]$$

$$n(0,t') = N_0\delta(t') \qquad [14]$$

where λ is the out-migration rate constant, Δ is the death rate constant, β is the in-migration rate, γ is the birth rate constant, N_0 is the initial number of people in the region, $\delta(t')$ is the Dirac delta function, and $N(t)$ is the total number of people in the region at time t (defined by the second equality in Eq. 13). Equation 12 states that the chronological time rate of change in the number of individuals per residence time interval dt' (left-hand term) equals the rate at which individuals age into this interval less those who age out of it (first right-hand term) less the number of individuals who die or leave the area (second right-hand term). Equation 13 states that the flux of people just entering the region at any time t, thus having a zero residence time, is equal to the constant rate of in-migration (β) plus the rate of entry of newborns. Equation 14 merely states that the number of people initially living in the area at the time of emission start-up is N_0, and that these people are all characterized by a zero residence time at $t = 0$.

The model may be solved for $n(t,t')$ by the method of characteristics in two time domains, $t' \geq t$, $t' < t$ (*17*). When birth and death rates are nearly equal, $\gamma = \delta$ and the residence time distribution is found to be

$$n(t,t') = N_0\delta(t' - t)e^{-(\lambda+\gamma)t} + e^{-(\lambda+\gamma)t'}H(t - t') \{\beta + \gamma N_0 e^{-\lambda(t-t')} + \frac{\beta\gamma}{\lambda}[1 - e^{-\lambda(t-t')}]\} \qquad [15]$$

where $H(x)$ is the Heaviside operator.

Expression for Toxic Response in a Migrating-Birthing-Dying Population

As described above, the population response at time t, $n_p(t)$, involves integrating over the toxic responses induced in each residence time cohort, i.e.,

$$n_p(t) = \int_0^t P(t',t)\, n(t,t')\, dt' + \int_0^t\int_0^{t''} P(t',t'') (\lambda + \Delta)\, n(t'',t')\, dt'dt'' \qquad [16]$$

where $P(t',t)$ is the probability that an individual will develop a toxic response over the exposure time $t - t'$ to t. The first integral accounts for the toxic cases remaining in the locale, and the second accounts for those cases which occurred in persons who died or moved to other geographical areas. (This formulation assumes that the toxic response itself is not fatal, as is the case with arsenical skin cancer.) For the case of constant dose rate in the geographical region and for the multistage model applied to low dose arsenic exposure, $P(t',t)$ can be identified as the low dose limit of Equation 4 with one stage dose-related,

$$P(t',t) = Ac_0t'^k \qquad [17]$$

where A is a grouped constant of a_i's and b_i's.

Magnitude of Migration Effect on Response Estimate

To assess the magnitude of migration and birth-death effects on response estimates, we determine the ratio R_M of the number of toxic cases in our geographical region when migration is taken into account to the number of cases when it is not. We assume that at the beginning of exposure, the region contains the steady state number of people $N_{ss} = \beta / \lambda$. R_M is thus

$$R_M = \frac{n_p(t)}{N_{ss}P(t,t)}$$

with $n_p(t)$ given by Equation 16 and $P(t,t)$ by Equation 17 with $t' = t$. After performing the integrations in Equation 16, one finds that

$$R_M = \exp(-y) + (2 + y)y^{-k}G(k + 1,y) - y^{-k}G(k + 2,y) \qquad [18]$$

where $y = (\lambda + \gamma)t$ and $G(a,x)$ is the incomplete gamma function

$$G(a,x) = \int_0^x t^{a-1}e^{-t}dt$$

Next we evaluate R_M for arsenic, whose k is 4, for a typical human population birth death rate, $\lambda = 1.43\%$/yr, and a range of out-migration rates λ. Values chosen for λ were 1.4%/yr, 4.5%/yr, and 12.9%/yr. The observation period for toxic response has been taken as 30 years (rather than lifetime). No other parameters were necessary since they cancelled out in forming the R_M ratio. The R_M values are tabulated in Table 3.

The R_M values in Table 3 show that unless migration effects are taken into account, estimates of arsenic toxicity may be overpredicted by an order of magnitude at

Table 3. Ratio of toxic responses with and without migration-birth-death included.[a]

Out-migration rate λ, %/yr	R_M
1.4	0.61
4.6	0.36
12.9	0.11

[a] Multistage, $k = 4$.

high migration rates and about threefold at more moderate migration rates. Had the dependence of arsenic toxicity on exposure time been much less, with k approaching unity, then R_M would also have been closer to 1 and migration effects would have become unimportant. Conversely, migration would have played a still larger role for k values above 4. Finally, it should be noted that these observations are quite general in that they apply identically to any substance describable by a Weibull dose-response relationship. This is suggested by Equation 17, which is a special case of the low dose Weibull A $c^m t^k$. Had m not been 1, the same R_M ratio would have been obtained since c^m would have cancelled in the numerator and denominator.

Summary

Both time-dependent administration schedules and pharmacokinetic transients have been identified as sources of time-variant exposure, although, because of their short time scale, pharmacokinetic transients (as opposed to their steady states) are expected to play a major role in risk estimation only for a limited number of substances or in short-term assays. It has been shown that, for one-hit and multihit models, rigorous estimates of toxic response may be obtained from time-averaged doses only. On the other hand, it was shown that the multistage and clonal two-stage models generally require explicit treatment of time-dependent tissue concentrations (local dose) or else large errors may be encountered, depending on the exact dosage pattern and the sensitivity of response to exposure time. For a substance, such as ethylene dibromide, which produces a response strongly sensitive to exposure time, an order of magnitude response error can be encountered even when a two-thirds lifetime exposure is averaged over a full lifetime. If arsenic is considered, a threefold error is still encountered, although the response to this substance is two powers less dependent on exposure time. It was also shown that the clonal two-stage model requires treatment of concentration time dependency during estimation of toxic response if errors similar to the multistage are to be avoided. In addition, response errors in this model were shown to be dose dependent due to the assumption of two dose-related stages. Finally, the introduction of time-variant exposure in epidemiological populations by migration and birth-death dynamics was examined for the magnitude of its effect on toxic response estimates. It was found that if these dynamics were ignored and populations were assumed static (a common assumption) overprediction of true response occurs. Furthermore, this overprediction was an order of magnitude for populations characterized by average birth and death rates, out-migration rates in excess of 5%/yr, and exposure to toxic agents with a moderate sensitivity of response to exposure time (e.g., those with a Weibull time-to-response exponent $\geqslant 4$).

REFERENCES

1. Whittemore, A., and Keller, J. Quantitative theories of carcinogenesis. SIAM Rev. 20: 1–30 (1978).
2. Lee, P. N. A model of experimental carcinogenesis and experiments to test it. Tobacco Research Council Review of Activities 1970–1974. London, 1975, pp. 28–32.
3. Day, N. E., and Brown, C. C. Multistage models and primary prevention of cancer. J. Natl. Cancer Inst. 64: 977–989 (1980).
4. Armitage, P., and Doll, R. A. two-stage theory of carcinogenesis in relation to the age distribution of human cancer. Br. J. Cancer 11: 161–169 (1957).
5. Fisher, J. C. Multiple-mutation theory of carcinogenesis. Nature 181: 651–652 (1958).
6. Crump, K. S., and Howe, R. B. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4: 163–176 (1984).
7. Lutz, R. J., Dedrick, R. L., Tuey, D., Sipes, I. G., Anderson, M. W., and Matthews, H. B. Comparison of the pharmacokinetics of several polychlorinated biphenyls in mouse, rat, dog, and monkey by means of a physiological pharmacokinetic model. Drug Metab. Dispos. 12: 527–535 (1984).
8. Hartley, H. O., and Sielken, R. L., Jr. Estimation of "safe doses" in carcinogenic experiments. Biometrics 33: 1–30 (1977).
9. Armitage, P. and Doll, R. The age distribution of cancer and a multi-stage theory of carcinogenesis. Br. J. Cancer 8: 1–12 (1954).
10. Tseng, W. P. Effect and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109–119 (1977).
11. Irgolic, K. Speciation of Arsenic in Water Supplies. Quarterly Progress Report, November 1, 1978–January 31, 1979. EPA Grant R-804774, Washington, DC, 1979.
12. National Cancer Institute. Bioassay of 1,2 Dibromoethane for Possible Carcinogenesis. Technical Report Series No. 86, DHEW Publication No. (NIH) 78-1336, 1978.
13. Environmental Protection Agency. Ambient Water Quality Criteria for Arsenic. Document EPA 440/5-80-021, Washington, DC 1980.
14. Bolten, J. G., Morrison, P. F., and Solomon, K. A. Risk-Cost Assessment Methodology for Toxic Pollutants from Fossil Fuel Power Plants. The Rand Corporation, R-2993-EPRI, Santa Monica, CA, 1983.
15. Moolgavkar, S. H., and Venzon, D. J. Two-event models for carcinogenesis: Incidence curves for childhood and adult tumors. Math. Biosci. 47: 55–77 (1979).
16. Moolgavkar, S. H., Day, N. E., and Stevens, R. G. Two-stage model for carcinogenesis: Epidemiology of breast cancer in females. J. Natl. Cancer Inst. 65: 559–569 (1980).
17. Bolten, J. G., Morrison, P. F., Solomon, K. A., and Wolf, K. Alternative Models for Risk Assessment of Toxic Emissions. The Rand Corporation, N-2261-EPRI, Santa Monica, CA, 1985.