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A GOMPERTZ AGE-SPECIFIC MORTALITY RATE MODEL OF AGING, HORMESIS, AND TOXICITY: DOSE–RESPONSE STUDIES*†

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I. INTRODUCTION

Why . . . should I marvel or let myself be frightened because one part is poison, and despise the other part too? . . . Who despises poison, knows not what is in the poison. . . . He who strikes the middle, receives no poison. . . . If you wish justly to explain each poison, what is there that is not poison? All things are poison, and nothing is without poison: the Dosis alone makes a thing not a poison.

—Paracelsus (1493–1541) [1]

In a previous series of papers [2–4], a generalized phenomenological model was developed characterizing mammalian mortality experience arising from aging, toxicity, and hormesis. From a mortality perspective, hormesis, or more properly longevity hormesis, refers to beneficial life-enhancing alterations in an organism's state, brought about by exposure to an otherwise toxic substance [3]. Although its mechanism is unknown, longevity hormesis has the following four characteristics: (1) It is apparently manifested at both low and high doses of toxicants. At higher doses, however, toxic manifestations may obscure beneficial hormetic activity. (2) Hormetic responses of like kind are elicited by seemingly unrelated stimuli (ionizing radiation, solvents, pesticides, etc.). (3) The response is reversible. Longevity hormesis is a generalized phenomenon that need be distinguished from a compound's beneficial or "proper" activity [5]. A proper action results when a substance enhances longevity through a specific and relatively unique biochemical mechanism for example, the actions of low doses of vitamin B-12, selenium, and exogenously produced antibodies. Conversely, longevity hormesis is a nonspecific response to unrelated stimuli. And unlike life prologation observed following caloric restriction in mammals, longevity hormesis does not act to enhance lifespan through a reduction in actuarial aging; that is, it does not slow the aging process per se [4, 5].

In this paper we apply our aging–toxicity–hormesis model to mammalian mortality data from groups of laboratory animals who received more than one dose of toxicant. Prior to model application, however, we summarize some of its basic features. Much of the theoretical development of this model has been discussed in great detail elsewhere [2–5], and therefore only salient features are reviewed here.

II. THEORY

Oh, come with old Kháyyam, and leave the Wise
To talk; one thing is certain, that Life flies;
One thing is certain, and the Rest is Lies;
The Flower that once has blown for ever Dies.

—Verse XXVI, Rubáiyát of Omar Khayyám [6]

Based on the work of Sacher and Brues [7–10], we assume the hazard function is an exponential function of the mean intensity of injury for a homogeneous mammalian population housed in a uniform environment and kept free of preventable disease. The hazard function is the probability of death over the interval $(x + dx)$, assuming survival to age x. The term injury denotes deleterious modification of vital system states [11]. A generalized, logarithmically transformed hazard function may be posited [5]:

$$G_x = G_0 + \varphi(x) \tag{1}$$

where G_x (termed the Gompertzian, Gompertz transformation, or Gompertz function) is the Napierian logarithm of the hazard function, G_0 (vulnerability parameter) is an extrapolated zero-age intercept, and $\varphi(x)$ is a unitless term representing population mean intensity of injury at age (or time) x. Consequently, $\varphi(x)$ is a weighted combination of several injury processes, summating and decrementing injury resulting from aging as well as from the detrimental and/or beneficial effects elicited through administration of exogenously administered substances. The vulnerability parameter (G_0), which is related to the vigor of the genotype in the environment, measures the initial vulnerability of the population to disease before the onset of aging and senescence; it represents an initial condition upon which the second law of thermodynamics can play [12].

In its simplest (linear) form, the Gompertz function is:

$$G_x = G_0 + ax \tag{2}$$

where a (a first-order aging rate constant) is a measure of intrinsic or actuarial aging [13]. Under the rigid experimental conditions imposed in mammalian risk assessment studies (homogeneous populations, well-controlled environments, nutritionally complete diets, and barrier facilities to prevent infections and other disease), the linear Gompertz function frequently characterizes mortality experience remarkably well [2–5]. Under the condition of constant-rate administration of an exogenous substance, we deduce a more complex Gompertz function incorporating postulated injury and hormesis terms [4]:

$$G_X = G_0 + (a + \gamma_D)x - \left[\frac{\lambda_D}{K}(1 - e^{-Kx})\right] \tag{3}$$

where γ_D is a first-order rate constant characterizing the irreversible component of exogenously induced injury at dose rate D, λ_D is a hybridized parameter proportional to the rate constant characterizing hormetic injury reduction at dose rate D, and K is a first-order rate constant for dissipation of the hormetic effect. In the absence of toxicity, $\gamma_D = 0$; and in the absence of hormesis, $\lambda_D = 0$. It is important to realize that Eq. (3) is phenomenological; that is, it was empirically deduced. In order for this relationship to have a particular form, the function was devised in an ad hoc fashion. Therefore, the parameters are a characteristic of the equation and *not necessarily* of the biological system. This is especially true given our simplifying assumptions (*vide infra*) as well as the fact that other mathematical functions may have worked equally well or better.

Embedded within Eq. (3) are several assumptions: (1) increments of nonreparable injury (exogenously induced) accumulate at a constant age-independent rate and summate with natural aging injury; (2) from an actuarial perspective, hormesis acts independently of any toxic manifestations in reducing mortality; (3) hormesis decrements injury (and mortality) at a constant age-independent rate; and (4) hormetic decrements to mortality dissipate by a first-order process (characterized by K). As noted earlier, the effects of hormesis [represented by the negative term on the right-hand side of Eq. (3)] should be differentiated from those of caloric restriction. In mammals, caloric restriction (under conditions of adequate nutrition) reduces a; this leads to improved survival, decreased body weight, and reductions in age-specific pathologies [5, 14–17]. The reduction in the Gompertz function from caloric restriction is permanent (the representative organism derives benefit throughout life). In contradistinction, the hormetic benefit is reversible; upon discontinuance of the hormetic stimulant, hormetic decrements in G_x dissipate at a first-order rate. Following discontinuation of dosage, and assuming time has progressed through at least 5 half-lives of K, the representative surviving organism derives virtually no actuarial benefit.

To demonstrate properties of Eq. (3), simulations are illustrated in Figs. 1 [4] and 2 [2]. In Fig. 1, curve C represents control animals. Curve A, with its attendant increase in slope, is observed only when toxicity is manifested. Curve E occurs only when hormesis is manifested; note the steady-state hormetic benefit that differentiates curves C and E at the latter time points. Curve D depicts the situation in which both toxicity and hormesis coexist. In this case, the benefits derived from hormesis are greater than the disadvantages from toxicity for the representative organism, out to at least 120 time units. Case B is

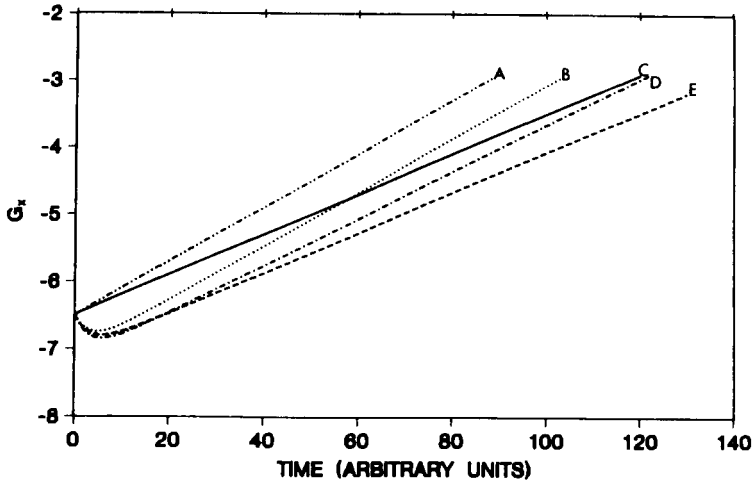

FIG. 1. Gompertz diagrams of Napierian logarithms of age-specific mortality rates versus time [simulated from Eq. (3)]: Curve C represents control animals; curve A assumes only toxicity; curve E assumes only hormesis; and curves B and D assume that both hormesis and toxicity coexist (with toxicity being more dominant in case B). See text for discussion. This figure was reproduced from Fig. 1 of Neafsey et al. [4] with permission of copyright owner (Marcel Dekker, Inc.).

analogous to case D, except that toxicity is greater; consequently, the detrimental effects of toxicity supercede the benefits from hormesis at earlier times.

Figure 2 illustrates the reversibility of hormesis. It shows Gompertz plots for control animals and those receiving a hormetic agent (possessing no toxicity) administered at a constant rate between 0 and 40 time units. Note that a steady state is rapidly achieved (10–40 time units) between the two functions. Upon discontinuance of the hormetic agent, however, the steady-state decrement in the Gompertzians dissipates exponentially.

The ability of Eq. (3) to satisfactorily characterize a broad array of mortality data sets has previously been demonstrated [4]. However, this was only done for exogenously administered agents given at a single, constant dose rate. In this paper, we extend our previous work to include data sets where the exogenous agent is given at more than one dose rate, to characterize both γ_D and λ_D as a function of dose rate.

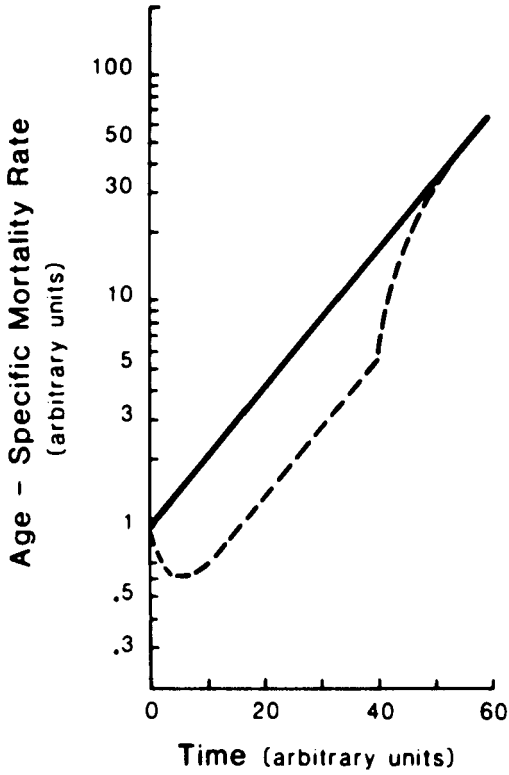

FIG. 2. Gompertz diagrams of age-specific mortality rates versus time (semilogarithmic plots). The solid line represents the control. The dashed line arises when chronic administration of a hormetic agent occurs from 0 to 40 time units but is discontinued thereafter. See text for discussion. Redrawn from Fig. 6 of Boxenbaum et al. [2] with permission of copyright owner (Marcel Dekker, Inc.).

While a broad array of mechanistic and empiric dose–response functions exist for such purposes (see, e.g., Refs. 18–21), we decided to employ the logarithmic-logistic function (also known as the sigmoid E_{max}, Hill equation, and generalized hyperbolic function). Our decision was somewhat empirical; dose–response functions with fewer parameters (e.g., logistic and E_{max} equations) frequently failed to provide satisfactory fits. Accordingly, γ_D and λ_D were computed from the following relationships [18]:

$$\gamma_D = \frac{\gamma_{max} D^T}{\left(\frac{1}{Q_T}\right) + D^T} \tag{4}$$

$$\lambda_D = \frac{\lambda_{max} D^H}{\left(\frac{1}{Q_H}\right) + D^H} \tag{5}$$

where γ_{max} and λ_{max} are the maximum toxic and hormetic responses, respectively; D is dose rate; and T, H, Q_T, and Q_H are constants. The larger the value of T, the more rapidly γ_{max} is approached with increasing D. Therefore, T may be viewed as a "shape" parameter. The value of Q_T helps define the range of D over which most responses (5–95% of γ_{max}) are observed. Therefore, Q_T may be viewed as a "scale" parameter. When $T = 1$, $\frac{1}{Q_T} = \frac{1}{2}\gamma_{max}$. Dose rates producing one-half of maximal responses are given by [18]:

$$\frac{1}{2}\gamma_{max} = Q_T^{\frac{1}{T}} \tag{6}$$

$$\frac{1}{2}\lambda_{max} = Q_H^{\frac{1}{H}} \tag{7}$$

The hyperbolic functions chosen for the dose response curves—Eqs. (4) and (5)—may surprise the reader. While longevity hormesis could conceivably have an easily defined maximum, it seems that toxicity would be less likely to necessarily have a hyperbolic shape. Toxicity could be linear or even supralinear before reaching a maximum. Therefore, all toxicity parameters are problematic.

While the logarithmic-logistic function can be derived from receptor theory (Hill equation), in which case parameter values have specific interpretations (e.g., T is the number of ligand molecules combining with each receptor), use of the logarithmic-logistic function in more complicated systems such as ours does not detract from its usefulness as an empirical descriptor of dose–response relationships [18–20]. Obviously, such factors as dosage form bioavailability and other pharmacokinetic variables will affect parameter values. Consequently, interpretation of parameter estimates in terms of receptor interaction is unwarranted and unreasonable. In particular, empirical use of the logarithmic-logistic

equation here should not be construed as lending support to the non-threshold view of toxicity. Given the complexity of these systems, the paucity and variability of data, as well as statistical problems encountered in curve-fitting procedures, there are no doubt numerous alternative models consistent with available data.

To investigate the properties of Eq. (3) used in conjunction with Eqs. (4) and (5), a variety of simulations were run [22]. It was empirically observed that we could arbitrarily divide families of curves (arising from different dose rates) into three types: (1) those predominantly or exclusively affected by hormesis; (2) those predominantly or exclusively influenced by toxicity; and (3) those in which toxicity and hormesis both have a significant impact. Figure 3 illustrates the case in which, while both toxicity and hormesis coexist, hormesis predominates. In contrast, Fig. 4 illustrates a case in which toxicity predominates over hormesis.

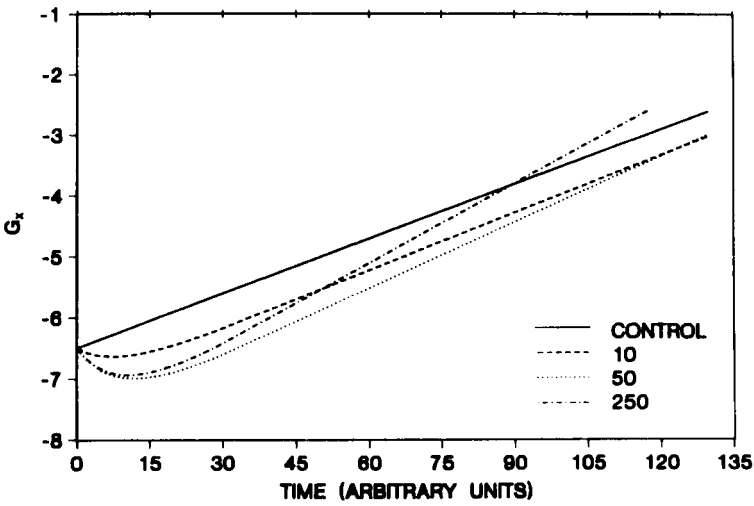

FIG. 3. Gompertz diagrams of Napierian logarithms of age-specific mortality rates versus time [simulated from Eqs. (3)–(5)]. Although both toxicity and hormesis coexist, the hormetic effect predominates over much or all of the time frame. See text for discussion. The doses were 0, 10, 50, and 250 (arbitrary) units. The parameters were $G_0 = -6.5$, $a = 0.03$, $\gamma_{max} = 0.02$, $T = 1$, $Q_T = 0.01$, $\lambda_{max} = 0.15$, $H = 2$, $Q_H = 0.01$, and $K = 0.116$. Not illustrated is the curve corresponding to a dose of 2. It was very slightly displaced downward from the control curve (but almost superimposable—and therefore not easily displayed).

coexist, hormesis predominates. In contrast, Fig. 4 illustrates a case in which toxicity predominates over hormesis. Figure 5 depicts a situation in which both toxicity and hormesis significantly impact on the curves.

In the sections that follow, we discuss sources of data, curve-fitting methodologies, and results of data analysis. It will be demonstrated that Eqs. (3)–(5) adequately characterize mortality experience in mammalian laboratory animal populations receiving chronic doses of certain toxic substances. Whereas we do not purport our proposed Gompertz function to characterize mortality data from all or even a majority of toxicity studies, we do see it as a useful heuristic in the advancement of our understanding of the interplay between hormesis and toxicity.

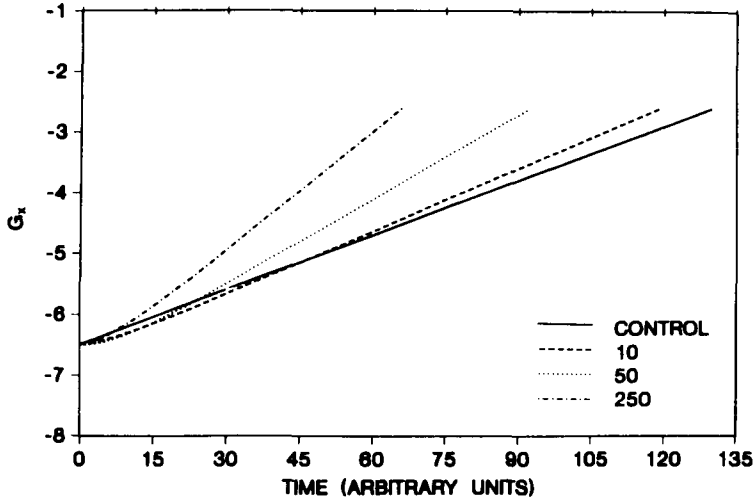

FIG. 4. Gompertz diagram of Napierian logarithms of age-specific mortality rates versus time [simulated from Eqs.(3)–(5)]. Although both toxicity and hormesis coexist, the toxic effect predominates over virtually all of the time period. See text for discussion. The doses were 0, 10, 50, and 250 (abitrary) units. The parameters were $G_0 = -6.5$, $a = 0.03$, $\gamma_{max} = 0.05$, $T = 1$, $Q_T = 0.01$, $\lambda_{max} = 0.05$, $H = 2$, $Q_H = 0.01$, and $K = 0.116$.

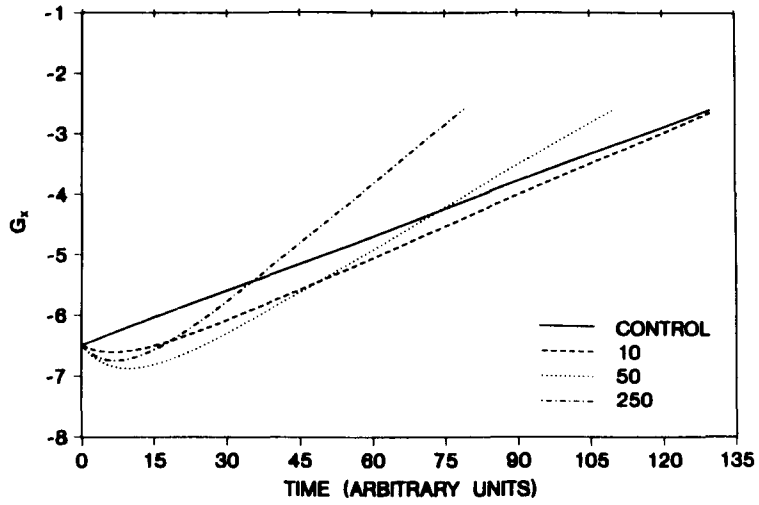

FIG. 5. Gompertz diagram of Napierian logarithms of age-specific mortality rates versus time [simulated from Eqs. (3)-(5)]. Both toxicity and hormesis significantly affect the curve patterns. See text for discussion. The doses were 0, 10, 50, and 250 (arbitrary) units. The parameters were $G_0 = -6.5$, $a = 0.03$, $\gamma_{max} = 0.05$, $T = 1$, $Q_T = 0.01$, $\lambda_{max} = 0.15$, $H = 2$, $Q_H = 0.01$, and $K = 0.116$.

III. METHODS

A. Data Aquisition

Mortality data from mammalian populations receiving chronic doses of toxic substances (at more than one dose level) were obtained from the periodical literature and from the National Toxicology Program (NTP) of the National Cancer Institute (NCI). (It is our intuitive estimate from going through these data sets that longevity hormesis exists in about 10-50% of all risk assessment studies.) To help simplify analysis (in an already highly parametized model), data were selected only if control population mortality experience could be characterized by the linear Gompertz function. This should not be construed as a requirement of the generalized model; on the contrary, toxicity and hormesis terms from Eq. (3) can be used in conjunction with any function used to describe a control population. Other requirements of data sets were: (1)

the experiment needed to be conducted at three or more dose rates; (2) dosing had to continue throughout most or all the postweaning study period; (3) each treatment group has to contain at least 50 animals (to ensure an adequate number of reliable data points); and (4) there needed to have been some visual evidence on the Gompertz plots that hormesis was operative—that is, curves needed to look like either B, D, or E of Fig. 1. Data sets meeting these criteria employed in the present analyses are summarized in Table 1. Table 2 reviews pathological observations and body weight gain data. Although there were some decreases in body weights (data set 3; see footnote *b* of Table 2), these appeared to occur randomly and were not believed to be of sufficient magnitude (−3% and −8%) to have significantly impacted on aging rate. The increases in body weights reported in Table 2 are believed a manifestation of longevity hormesis; as previously reported [4], longevity hormesis is often associated with body weight gain.

B. Data Manipulation

Cumulative mortality or survival data were used to calculate estimates of age-specific mortality rate. The following equations were employed [9]:

$$P_i = \frac{N_i - d_i}{N_i} \tag{8}$$

$$\Omega_x = -\left(\frac{1}{u_i}\right) \ln P_i \tag{9}$$

where P_i is the fraction of the population surviving the age interval u_i, N_i is the number of survivors at the beginning of the interval, d_i is the number of deaths over the interval, and Ω_x is an estimate of the age-specific mortality rate. In the context of this paper, Ω_x (estimated age-specific mortality rate) is used to approximate the hazard function. Consequently, G_x is used to denote theoretical (error-free) values of the Napierian logarithm of the hazard function, whereas ln Ω_x is used to denote an estimate of G_x. Estimated Gompertzians (ln Ω_x values) were calculated at times x values) corresponding to midpoints of the intervals. On occasion, contiguous data were pooled to ensure deaths over an interval represented at least 4% of initial cohort numbers (but never less than 2 deaths). Statistical weights (W) for ln Ω_x values were take as estimates of the reciprocal of variance (V) [9, 22]:

TABLE 1

Data Sets: Gompertz Aging, Hormesis, and Toxicity Model

Data set no.	Compound	Doses	Route	Species	Sex	Ref.
1	Methylene chloride	500, 1500, 3500 ppm (6 h/day, 5 days/wk)	Inhalation	Syrian golden hamsters	Female[a]	Burek et al. [23]
2	Methylene chloride	500, 1500, 3500 ppm (6 h/day, 5 days/wk)	Inhalation	Sprague–Dawley rats	Female[a]	Burek et al. [23]
3	Gamma-radiation	0.11, 1.1, 2.2, 4.4, 8.8 rad/day[b]	Whole-body exposure	LAF1 mice	Male and female (pooled)[c]	Lorenz et al. [24]
4	Hexachlorobenzene	0.32, 1.6, 8, 40 ppm	Diet	Sprague–Dawley rats (F1 generation)	Female[d]	Arnold et al. [25]
5	DDT	2, 10, 50, 250 ppm	Diet	CR-1 mice (F1 generation)	Female[e]	Tomatis et al. [26]
6	DDT	2, 10, 50, 250 ppm	Diet	CF-1 mice (F1 generation)	Male[e]	Tomatis et al. [26]

[a]The investigators did not report mortality data for male animals.

[b]Daily doses were administered over an 8-h period.

[c]As the investigators found no statistically significant differences in survival between the sexes, their data were pooled.

[d]Whereas the presence of both hormesis and toxicity was suggested by visual inspection of Gompertz functions for male F1 Sprague–Dawley rats, these effects were relatively minor compared to those in female F1 animals. Consequently, these male data are not reported. Data from F0 male Sprague–Dawley rats fed vitamin A and hexachlorobenzene were precluded from analysis, since 6- and 12-month sacrifices perturbed the mortality curves.

[e]Data from male and female CF-1 mice (P generation) are not reported here; while the presence of hormesis and toxicity was suggested from visual inspection of the Gompertz functions, the magnitude of these effects was considerably less pronounced than with the F1 generation.

TABLE 2

Weight Gain and Pathology Summary

Data set Number	Compound (species)	Weight gain of exposed animals (relative to controls)	Pathology of exposed animals (Relative to controls)
1	Methylene chloride (female hamsters)	NS[a]	No end-organ (liver) toxicity. Decreased age-associated liver and renal changes.
2	Methylene chloride (female rats	NS[a]	Increased benign mammary tumors (not statistically significant). Increased liver histopathological changes. Decrease age-associated renal pathology. Decreased pituitary tumors.
3	Gamma-radiation (male and female mice)	—[b]	Increased lymphoid tumors in high doses (4.4, 8.8 rad).
4	Hexachlorobenzene (female rats)	NS[a]	Decreased nonneoplastic lesions, mammary carcinomas in low-dose group (0.32 ppm). Increased neoplastic liver tumors in high-dose group (40 ppm).
5	DDT (female mice)	Increased[c]	Increased benign liver tumors at earlier age in high-dose group (250) ppm.
6	DDT (male mice)	Increased[d]	Increased benign liver tumors at earlier age in high-dose group (250 ppm).

[a]Authors reported no statistically significant differences in body weight gain.

[b]With the exception of 0.11 rad/day exposed females and 8.8 rad/day exposed males, all irradiated groups had increased body weight compared to controls at 64 weeks. Compared to controls, body weights for exposed mice ranged from approximately −3% (8.8 rad/day) to +25% (1.1 rad/day) in males, and −8% (0.11 rad/day) to +19% (2.2 rad/day) in females.

[c]Approximately 6–12% at 52 weeks and 3–9% at 78 weeks.

[d]Approximately 12–17% at 52 weeks and 16 –17% at 78 weeks.

$$W = \frac{1}{V} \cong \frac{[N_i P_i (\ln P_i)^2]}{(1 - P_i)} \tag{10}$$

C. Curve-Fitting Methodologies

Equation (3) was simultaneously fit to $\ln \Omega_x - x$ data pairs from all dose rates. Values for $\ln \Omega_x$ were weighted in accordance with Eq. (10). Equations (4) and (5) were incorporated as part of the subroutine used to define the function [Eq. (3)]. Two independent variables were used: age at the midpoint of the interval (x) and dose rate (D). For control animals, D was set equal to zero.

The nonlinear least squares computer program PCNONLIN [27, 28] was employed; it was used in conjunction with an IBM-PC desk-top microcomputer equipped with an 8087 math coprocessor chip. The Nelder-Mead [29] simplex algorithm was used to search the parameter space. In the final curve fit, iterated parameters were $\ln \Omega_0$, a, γ_{max}, T, Q_T, λ_{max}, H, Q_H, and K.

Throughout each step of the curve-fitting procedure, previously estimated parameter values were used as initial estimates for subsequent operations. Estimates of $\ln \Omega_0$ and a were initially obtained from weighted linear least squares analysis [30] of control data. Equation (3) was then fit to individual curves at each dose rate; while iterating γ_D, λ_D, and K, G_0 and a were held constant. See our previous work in this area [4] for the exact procedure. This provided estimates of γ_D and λ_D as a function of dose rate; a dose-independent estimate of K was also obtained. γ_D was next plotted against D to provide a visual estimate of γ_{max}. Based on the following linearization [18], estimates of T and Q_T were then obtained from graphical analysis:

$$\ln\left(\frac{\gamma_D}{\gamma_{max} - \gamma_D}\right) = T \ln D + \ln Q_T \tag{11}$$

A somewhat more refined estimate of γ_{max} was then obtained from additional graphical analysis; this was based on the extrapolated intercept value from the following equation [18]:

$$\left(\frac{1}{\gamma_D}\right) = \left(\frac{1}{Q_T \gamma_{max}}\right)\left(\frac{1}{D^T}\right) + \left(\frac{1}{\gamma_{max}}\right) \tag{12}$$

It is well known that double reciprocal plots can cause statistical abberations (see Ref. 31, for example). Therefore the use of Eq. (12) may have been unnecessary and possibly detrimental; on the other hand, we

have some empirical observations that lead us to believe that judicious use of Eq. (12) may have been somewhat useful in our present analysis. (Overall, our experience with this highly parametized model leads us to conclude that, with the exception of $\ln \Omega_0$ and a, precise estimates of the remaining parameters cannot possibly be ascertained, regardless of methodology—*vide infra*). An analogous procedure was used to obtain initial estimates for λ_{max}, H, and Q_H. Equation (3) was then fit simultaneously to all dosed animal data sets [using Eqs. (4) and (5) in the subroutine]; $\ln \Omega_0$, a, γ_{max}, λ_{max}, and K were all held constant, while Q_T, T, Q_H, and H were iterated. A final curve fit was performed utilizing all data and iterating all 9 parameters.

Goodness-of-fit was satisfied for all curve fits by their meeting each of the following three criteria [4]: (1) visual inspection of plots of weighted residuals versus a indicated relatively good randomness of scatter of data points about fitted curves [32]; (2) visual inspection of data points ($\ln \Omega_x - x$ pairs) about the regression lines indicated relatively good randomness-of-scatter [33]; and (3) in the chi-square test, computed χ^2 values were less than tabulated values ($a = 0.05$) [34].

D. Ancillary Parameters

Doses producing 50% of the maximum toxic and hormetic responses were calculated from Eqs. (6) and (7), respectively; computer-estimated parameters were used in these calculations.

Indices of the hormetic and toxic effects were calculated as follows [4]:

$$\text{Hormesis index} = \frac{\left(\frac{\lambda_D}{K}\right)}{-\ln \Omega_0} \times 100 \tag{13}$$

$$\text{Toxicity index} = \frac{\gamma_D}{a} \times 100 \tag{14}$$

Times corresponding to survival percentiles (50% and 25% survival) for control and treated animals were calculated numerically (see Appendix A of Neafsey et al. [4] for the procedure). The doses corresponding to maximum survival times (50th and 25th percentiles) were derived from computer-generated tables of dose versus survivorship percentile times. Survival times on these tables were only accurate to the nearest

0.5 week. Doses at which survival times decreased relative to controls were determined in a similar manner (see Table 7 in the next section).

IV. RESULTS AND DISCUSSION

Initially a few general comments are presented regarding data in the tables. Then to better focus on properties of the model and conclusions about the data, each data set is discussed individually.

Table 3 summarizes parameter estimates for all data sets. In the first four data sets, the model could be simplified; that is, parameters could be reduced (*vide infra*). In general, $\ln \Omega_0$ and a values could be estimated with reasonable precision (i.e., low % of CVs). This, however, cannot be said for the remaining parameters. Percent CV values from several hundred to tens of million are observed. As discussed elsewhere [33], in a system with this many parameters, this is *not* a reflection of the quality of the data or how well the model characterizes the data. On the contrary, it indicates that a wide range of parameter estimates would equally well characterize the data. The model is consistent with the data, but many of its parameters cannot be determined with any degree of precision. In many cases, this results from extrapolation to regions well beyond the range of the data (e.g., γ_{max} may be estimated from data at relatively low doses). Therefore, extreme caution needs to be exercised if parameter estimates are used for purposes other than data characterization (within the observed dose range) or for assessing the adequacy of the model per se. Nonetheless, as the calculations of median (50%) or 25% survival times depend only on the shapes of the Gompertz curves, and these shapes are well characterized by the parameters, a reasonable degree of accuracy and precision may be expected (provided the survival times are not extrapolated to dose levels beyond the range of the data).

Table 4 lists the doses producing 50% of maximum toxic and hormetic responses. Some of these values were determined with reasonable precision, while others (e.g., methylene chloride) were not. The reasons for imprecision are those discussed in the context of Table 3 (*vide supra*).

Table 5 lists hormesis and toxicity indices at λ_{max} and γ_{max} values, respectively. Their precision is therefore related to the precision of λ_{max} and γ_{max}. The hormesis index is a relative measure of hormesis, in the absence of toxicity. The toxicity of index is a relative measure of toxicity, in the absence of hormesis. An interesting observation is that the toxicity index generally far exceeds the hormesis index; the frequent ascendancy of toxicity over hormesis (coupled with the reversibility of hormesis) helps

TABLE 3

Parameter Estimates of the Aging, Hormesis, and Toxicity Model[a]

Data set number	Compound (species)	ln Ω_0 (%CV)[c]	a (%CV)	γ_{max} (%CV)	Q_T (%CV)	T (%CV)	λ_{max} (%CV)	Q_H (%CV)	H (%CV)	K (%CV)	χ^2 p value[b]
1	Methylene chloride (female hamsters)	−7.38 (3.50)	0.0566 (4.86)	—[d]	—[d]	—[d]	0.609 (1680)	0.00240 (1100)	0.528 (1980)	0.116[e] (246)	$0.9 < p < 1.0$
2	Methylene chloride (female rats)	−8.19 (3.62)	0.0552 (5.85)	0.0359 (932)	2.09×10^6 (5×10^7)	1.49 (209)	—[f]	—[f]	—[f]	—[f]	$0.9 < p < 1.0$
3	Gamma-radiation (male and female mice)	−7.52 (3.06)	0.0390 (7.27)	0.376 (1070)	0.0218 (1060)	0.648 (72.5)	0.0785 (1280)	—[g]	—[g]	0.174 (1310)	$0.9 < p < 1.0$
4	Hexachlorobenzene[h] (female rats)	−7.70 (5.27)	0.044 (9.94)	0.0106 (53.8)	17.2 (662)	2.83[i] (204)	0.324 (3.58×10^5)	—[g]	—[g]	0.380 (3.58×10^5)	$0.9 < p < 1.0$
5	DDT (female mice)	−6.52 (6.41)	0.0316 (14.6)	0.0179 (60.3)	0.00837 (799)	1.33 (167)	0.0784 (212)	0.00879 (874)	2.97[i] (196)	0.116[e] (235)	$0.9 < p < 1.0$
6	DDT (male mice)	−6.93 (5.29)	0.0373 (11.6)	0.0214 (127)	0.0116 (666)	1.08 (207)	0.0705 (279)	0.00167 (767)	2.73[i] (1172)	0.116[e] (286)	$0.9 < p < 1.0$

[a]The parameters in Ω_0, T, and H are unitless; parameters with units are a: weeks^{-1}, γ_{max}: weeks^{-1}, Q_T: ppm^{-T}, except for data set 3 where it is (R/day)$^{-T}$, λ_{max}: weeks^{-1}, Q_H: ppm^H and K: weeks^{-1}.

[b]A p value greater than 0.05 generally indicates consistency with the proposed distribution.

[c]Parameter estimate percent coefficient of variation; when this number is large, it indicates that any parameter estimate in a relatively large region of parameter space results in about an equally good fit to the data.

[d]As toxicity was not observed with the Gompertz plots, these parameters were omitted from the model.

[e]To ensure a parameter value consistent with previous work [4], the lower limit of this parameter was set to 0.116 during curve fitting.

[f]As hormesis not observed with the Gompertz plots, these parameters were omitted from the model.

[g]The logarithmic-logistic function was not applicable to the hormetic response in this data set, as a maximal response was apparent at the lowest dose; consequently, λ_D was assumed constant throughout the observed dose range.

[h]The first data point of the 1.6 ppm dose curve was eliminated from the curve fit (see text for discussion).

[i]To ensure a reasonable parameter value (not too large), the upper limit of this parameter was set to 3.00 during curve fitting.

TABLE 4

Doses (ED_{50}) Producing 50% of Maximum Toxic and Hormetic Responses[a]

Data set number	Compound (species)	Hormetic ED_{50} (%CV)	Toxic ED_{50} (%CV)
1	Methylene chloride (female hamsters)	9.2×10^4 ppm (4.3×10^{14})	—[b]
2	Methylene chloride (female rats)	—[b]	6.6×10^3 ppm (6.3×10^6)
3	Gamma-radiation (male and female mice)	—[b]	360 rad/day (7.5×10^5)
4	Hexachlorobenzene (female rats)	—[b]	0.37 ppm (53.0)
5	DDT (female mice)	4.93 pppm (298.0)	36.4 ppm (75.8)
6	DDT (male mice)	10.4 ppm (110.0)	61.0 ppm (252.0)

[a]ED_{50} values were calculated from Eqs. (6) and (7) using parameter estimates from Table 3. The %CV values in parentheses represent ED_{50} percent coefficients of variation (calculated by the computer program used for the curve fits).

[b]Not applicable (see Table 3 and text).

explain why net toxicity is so often observed in high-dose risk assessment studies.

Table 6 provides median (50%) and 25% survival times. As noted previously, these values depend for their accuracy (and precision) only on a satisfactory characterization of the corresponding Gompertz functions. Since the curve fits were satisfactory (*vide infra*), the values reported in Table 6 may be considered well estimated.

Table 7 reports theoretical (calculated) doses producing maximal survival times. Except in those cases where the doses fall outside the experimental dose range, reasonable estimates may be expected. The numerical approximation procedure includes an error, and this is so indicated. Of particular interest to the toxicologist (included in Table 7) is

TABLE 5

Hormesis and Toxicity Indices at λ_{max} and γ_{max} Values, Respectively

Data set number	Compound (species)	Hormesis Index (%)	Toxicity Index (%)
1	Methylene chloride (female hamsters)	71[a]	—[b]
2	Methylene chloride (female rats)	—[c]	65[a]
3	Gamma-radiation (male and female mice)	6.0	964[a]
4	Hexachlorobenzene (female rats)	11	24
5	DDT (female mice)	10	57
6	DDT (male mice)	8.8	57

[a]Above the experimental dose range.
[b]Toxicity not observed.
[c]Hormesis not observed.

the dose beyond which toxic detriment surpasses hormetic benefit. One might wish, for example, to set a standard (maximum exposure rate) at that dose which just barely decreases median or 25% survival. For gamma-radiation in mice (data set 3), these values are 0.7 and 0.5 R/day, respectively. When both hormesis and toxicity are present, the threshold toxic dose corresponding to 25% survival will generally be less than that for 50% survival.

A. Data Set 1: Methylene Chloride; 500–3500 ppm Inhalation; Female Syrian Golden Hamsters

Methylene chloride (dichloromethane) is a volatile liquid used as a paint remover, degreasing solvent, aerosol propellant, and grain fumigant [35]; it is readily absorbed through intact skin. The U.S. Occupational Safety and Health Administration (OSHA) upper limit for

TABLE 6

Median and 25th Percentile Survival Times[a]

Data set number	Compound (species)	Dose	Time (weeks) at survival percentiles	
			Median	25%
1	Methylene chloride (female hamsters)	0 ppm	73	86
		500 ppm	79 (+7.6)	91 (+5.8)
		1500 ppm	83 (+14)	95 (+10)
		3500 ppm	87 (+19)	99 (+15)
2	Methylene chloride (female rats)	0 ppm	89	101
		500 ppm	88 (−1.1)	99.5 (−1.5)
		1500 ppm	84 (−5.1)	95.5 (−5.4)
		3500 ppm	78 (−12)	88.5 (−12)
3	Gamma-radiation (male and female mice)	0 rad	99.5	116.5
		0.11 rad	107 (+7.5)	123.5 (+6.0)
		1.1 rad	95 (−4.5)	109 (−6.4)
		2.2 rad	87.5 (−12)	100.5 (−14)
		4.4 rad	79 (−21)	90.5 (−22)
		8.8 rad	70 (−30)	79 (−32)
4	Hexachlorobenzene (female rats)	0 ppm	96	111
		0.32 ppm	106.5 (+11)	121 (+9.0)
		1.6 ppm	97 (+1.0)	109.5 (−1.4)
		8.0 ppm	96.5 (+0.5)	109 (−1.8)
		40 ppm	96.5 (+0.5)	109 (−1.8)
5	DDT (female mice)	0 ppm	87	108
		2 ppm	87.5 (+0.6)	108 (0)
		10 ppm	99 (+14)	118.5 (+9.7)
		50 ppm	86.5 (−0.6)	102.5 (−5.1)
		250 ppm	78.5 (−9.8)	92.5 (−14)
6	DDT (male mice)	0 ppm	88.5	106.5
		2 ppm	87.5 (−1.1)	105.5 (−0.9)
		10 ppm	91 (+2.8)	108 (+1.4)
		50 ppm	87.5 (−1.1)	102 (−4.2)
		250 ppm	77.5 (−12)	90 (−15)

[a]Survival times were calculated from the parameters listed in Table 3 and were rounded off to the nearest 0.5 weeks. Numbers in parentheses are percent differences relative to controls. As these times depend only upon the shapes of the Gompertz functions, and no dose extrapolations were involved, these values may be considered reasonably accurate.

TABLE 7

Theoretical Doses Producing Maximal Survival Times and Threshold Doses Above Which Survival Times Decrease Relative to Controls[a]

Data set number	Compound (species)	Maximal survival time doses[b]		Threshold doses for decreased survival[b]	
		50% survival	25% survival	50% survival	25% survival
1	Methylene chloride (female hamsters)	5.6×10^7 ppm ± 10.7%[c] (43%)[c]	5.6×10^7 ppm ± 10.7%[c] (43%)[c]	—[d]	—[d]
2	Methylene chloride (female rats)	—[e]	—[e]	> 0 ppm	> 0 ppm
3	Gamma-radiation (male and female mice)	⩽ 0.11 rad/day[f] (⩾ 7.5%)[g]	⩽ 0.11 rad/day[f] (⩾ 6.0%)[g]	0.7 rad/day ± 14.3%	0.5 rad/day ± 20%
4	Hexachlorobenzene (female rats)	⩽ 0.32 ppm[h] (⩾ 11%)[j]	⩽ 0.32 ppm[h] (⩾ 9.0%)[j]	—[i]	1.1 ppm ± 9.1%
5	DDT (female mice)	10 ppm ± 30% (14%)	9 ppm ± 11.1% (10%)	47 ppm ± 2.1%	34 ppm ± 2.9%

6	DDT (male mice)	18 ppm ± 27.8% (3.3%)	17 ppm ± 17.6% (2.8%)	53 ppm ± 1.9%	34 ppm ± 5.9%

[a]All values were numerically approximated from parameters in Table 3. Consequently, any problems with accuracy and precision of revelant parameter estimates will be carried over into these calculations.

[b]Where applicable, ± values indicate the range of numerical error in the approximation. Numbers in parentheses represent percent increases over controls.

[c]Both the survival time and % change correspond to a dose much greater than that administered experimentally; i.e., these numbers were extrapolated values with virtually no accuracy and/or precision. They are therefore reported only to illustrate application of methodology (see text).

[d]Not applicable, as toxicity was not observed over the dose range investigated.

[e]Not applicable, as hormesis was not observed over the dose range investigated.

[f]A maximum hormetic response was observed over the entire dose range investigated; consequently maximum survival times would have been observed at doses equal to or less than the lowest dose studied, i.e., 0.11 R/day or less (see Table 3).

[g]The maximum percent increase in survival is equal to or greater than that from the response at the lowest experimental dose, 0. 11 R/day (see Table 3).

[h]A maximum hormetic response was observed over the entire dose range investigated; consequently maximum survival times would have been observed at doses equal to or less than the lowest dose studied, i.e., 0.32 ppm (see Table 3).

[i]Fluctuations in median survival times were minimal; consequently an accurate estimate of the threshold dose could not readily be obtained.

[j]The maximum percent increase in survival is equal to or greater than that from the response at the lowest experimental dose, 0.32 ppm (see Table 3).

8-h occupational exposure is 500 ppm; the present American Congress of Governmental Industrial Hygienists—Threshold Limit Value is 100 ppm, but there is a notice of intended change to reduce it to 50 ppm.

Data from inhalation studies were analyzed here [23]. Animals were approximately 8 weeks of age when entered into the study. Figure 6 illustrates the Gompertz plots and curve fits. It is readily apparent that toxicity, if present, cannot be detected. Consequently, Eq. (3) was fitted to the data omitting γ_D terms. It is likewise apparent that, in general, as exposure concentrations increased, the Gompertzians decreased. This is reflected in Fig. 7, which illustrates the increase in hormesis index as a function of dose. Given that a 4 parameter system term (comprising λ_{max}, Q_H, H, and K) was used to characterize response from an experiment employing 4 dose levels (including the control animals), and furthermore that these dose levels did not encompass a wide range of exposure concentrations, it was not possible to estimate the aforementioned parameters with any reasonable precision (see Table 3). This is also reflected in the extrapolated hormetic ED_{50} value (92,000 ppm). Obviously, there is insufficient information in the dose region

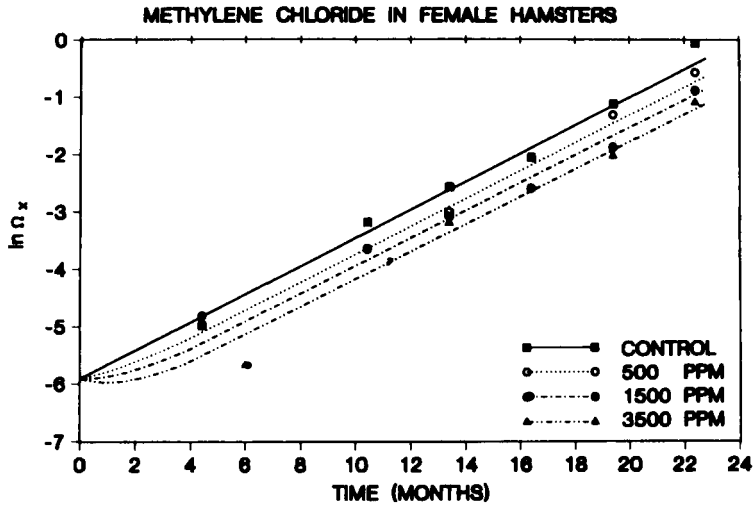

FIG. 6. Methylene chloride (500–3500 ppm inhalation) in female Syrian golden hamsters (data set 1): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. Methylene chloride exposure was begun at 8 weeks of age and continued for an additional 2 years. Time on the ordinate refers to that period following initiation of exposure. Survival data were obtained from Burek et al. [23].

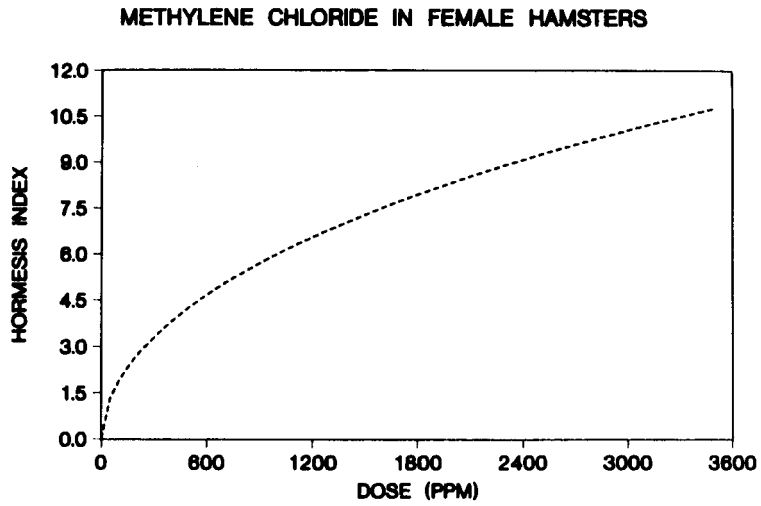

Fig. 7. Hormesis index as a function of dose in female Syrian golden hamsters (data set 1) exposed by inhalation to methylene chloride.

studied to extrapolate system behavior; this would be true even if methylene chloride exerted no toxicity whatsoever at higher doses.

Interestingly, exposure of these hamsters to 3500 ppm methylene chloride (7 times the legal exposure limit permitted for humans by OSHA) increased their median survival by 19% (Table 6). Since we do not know if humans respond in like manner, the significance of this observation cannot be gauged at the present time. This brings us to the next data set, in which we find female rats responding quite differently than female hamsters.

B. Data Set 2: Methylene Chloride; 500–3500 ppm Inhalation; Female Sprague-Dawley Rats

In the previous data set (female hamsters), methylene chloride exposure was found to elicit hormesis but no observable toxicity. In this data set with female rats, the situation is reversed. Visual inspection of Fig. 8 indicates only toxicity. Consequently, Eq. (3) was fit to the data omitting the hormetic term. As with data set 1, precision is lacking with logarithmic-logistic function parameters (γ_{max}, Q_T, and T). The low estimate of Q_T (2.09×10^{-6}) leads to a relatively large ED_{50} value (6600

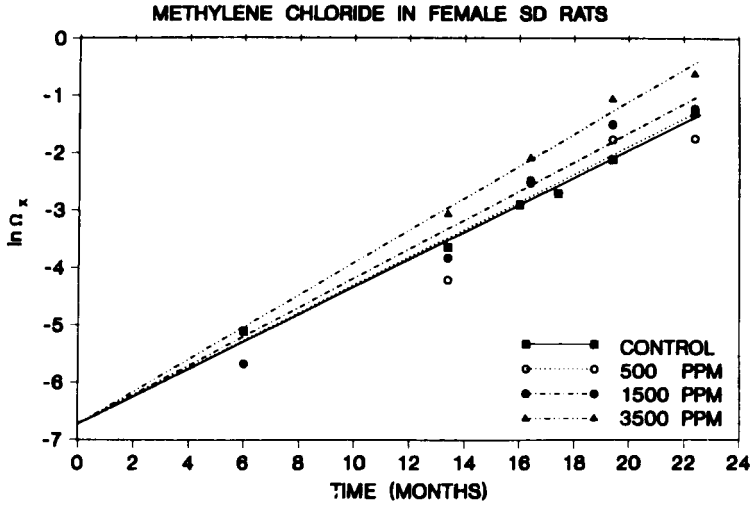

FIG. 8. Methylene chloride (500–3500 ppm inhalation) in female Sprague-Dawley rats (data set 2): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. Methylene chloride exposure was begun at 8 weeks of age and continued for an additional 2 years. Time on ordinate refers to that period following initiation of exposure. Survival data were obtained from Burek et al. [23].

ppm, see Table 4). As with all the logarithmic-logistic function parameters, this ED_{50} value also lacks precision. Figure 9 illustrates a plot of toxicity index versus dose. Over the dose range investigated, toxicity was modest; at the 3500 ppm dose, median survival time was reduced 12% (Table 6). However, since only toxicity was observed, and dose (>0 ppm) should in theory decrease 50% and 25% survival times (see Table 7).

Data sets 1 and 2 offer an instructive example of one of the many risk assessment dilemmas. Given that opposite effects are observed in female rats and hamsters, how does one extrapolate low exposure risk (if it exists) to man? Although some very elegant mathematical models have been developed for this purpose, they are so dependent on unsubstantiated and/or unreasonable assumptions that their conclusions are equivocal. Until we know whether a man qualitatively resembles a hamster or a rat in his response to methylene chloride (or neither), quantitative extrapolations of human risk must be viewed cautiously.

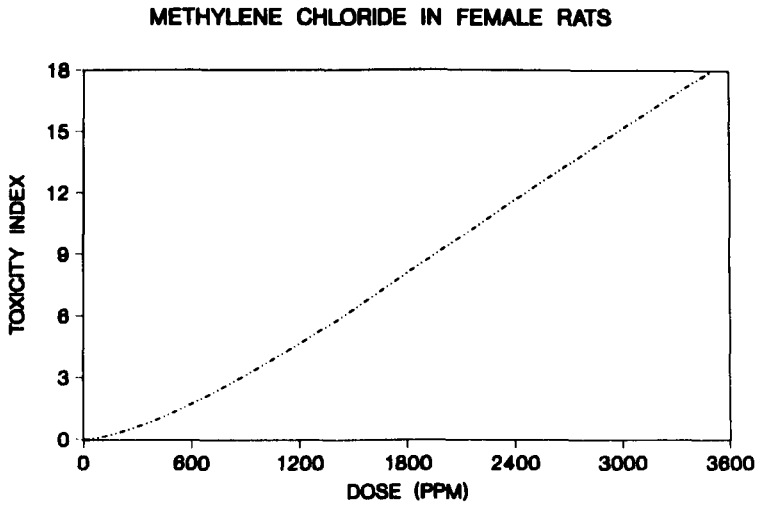

Fig. 9. Toxicity index as a function of dose in female Sprague-Dawley rats (data set 2) exposed by inhalation to methylene chloride.

C. Data Set 3: Gamma-Radiation; 0.11-8.8 rad/day; Male and Female LAF1 Mice

Gamma-rays are photons of electromagnetic radiation which are much more penetrating than alpha- or beta-particles [36]. From a 30-mg sample of radium, Ernest Rutherford (1871-1937) was able to detect more than 30 cm penetration into iron. Despite its potential for toxicity, Henry [37] reported as early as 1961 that "the preponderance of data better supports the hypothesis that low chronic exposures [to radiation] result in an increased longevity than it supports the opposite hypothesis of a decreased longevity." Nonetheless, even today there is a great reluctance on the part of most radiation scientists to attribute beneficial health effects to low doses of radiation. In one recent epidemiological study [38] in which standardized cancer mortality ratios for areas in the vicinity of nuclear installations were significantly less than for those of control areas, the authors stated the lower mortality from cancer in the vicinity of nuclear installations "is likely to be due to a protective effect of ionizing radiation and suggests that, despite the efforts that were made to choose comparable control areas, there were non-installation differences between the populations relevant to the risk of dying from one or other type of cancer."

Figure 10 illustrates Gompertz plots for mice exposed to varying doses of gamma-radiation. At 0.11 rad/day, the hormetic effects enhanced survival; toxic manifestations, however, canceled hormetic benefit at the higher doses. The logarithmic-logistic function characterizing hormesis could be simplified in this analysis. By assuming λ_{max} was reached at the lowest dose (0.11 rad/day), curve fits were obtained with essentially identical goodness-of-fits as when using the logarithmic-logistic function. Increasing doses therefore only enhanced toxicity in a dose-dependent fashion (see Fig. 11, which illustrates plots of the hormesis and toxicity indices as a function of dose). The extent of potential toxicity may be gauged by the large toxic ED_{50} value (360 rad/-day, Table 4); unfortunately, this estimate is outside the experimental dose range and has poor precision. Although precision is lacking in the estimates of γ_{max} and λ_{max}, Table 5 indicates a large disparity between maximum toxicity and hormesis indices (approximately 160 to 1). At the highest experimentally used dose level (8.8 rad/day), median survival time

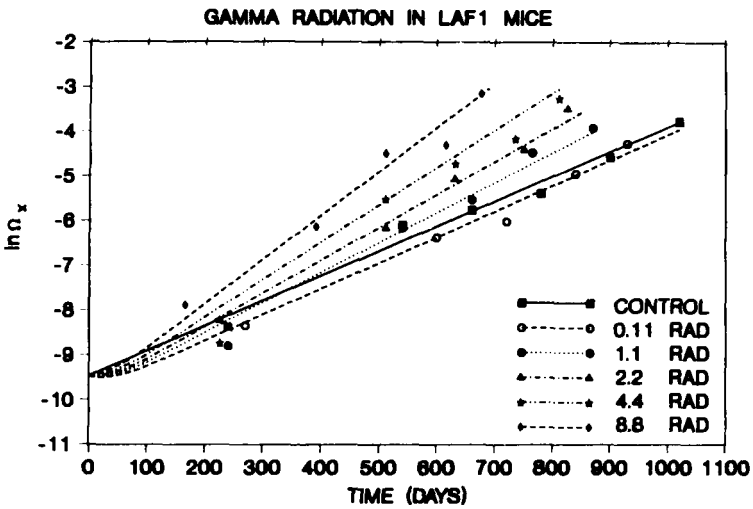

FIG. 10. Gamma-radiation (0.11–8.8 rad/day) in male and female LAF1 mice (data set 3): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. Gamma-radiation was begun at about 70 days of age and continued throughout life (daily doses were administered over 8-h intervals). Time on the ordinate refers to that period following initiation of exposure. Survival data were obtained from Lorenz et al. [24].

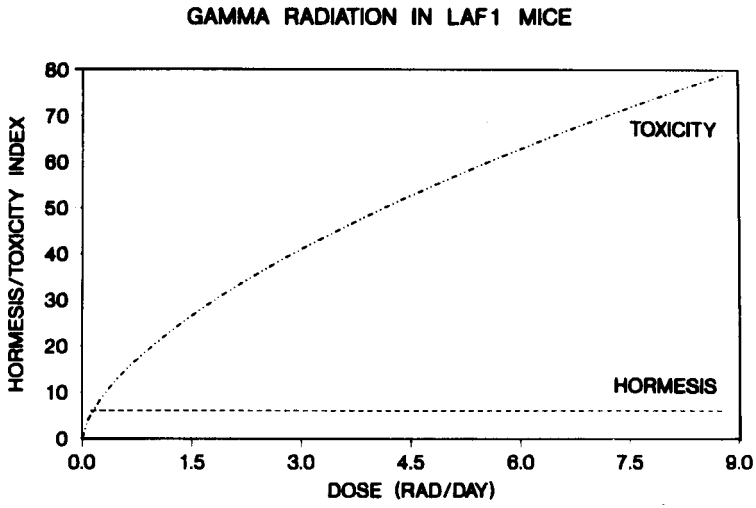

FIG. 11. Hormesis and toxicity indices as a function of dose in male and female mice (data set 3) receiving daily doses of gamma-radiation.

was reduced 30% (Table 6). However, one need only go beyond 0.7 rad/day (see Table 7) to have reduced median survival time (or 0.5 rad/-day to reduce the 25th percentile of survival).

In an attempt to clarify the observation of life prolongation raised in their initial study, Lorenz et al. [39] conducted a second study. Beginning at 1 month of age, groups of LAF1 mice were exposed to 0.11 rad/day (over 8 h) of gamma-radiation for duration of life; control animals were also studied. Unlike the previous study, only irradiated males lived longer (there was no difference between control and irradiated females). Enhanced longevity in male animals was also associated with enhanced body weight 20–90 weeks into the study. Figure 12 illustrates data and curve fits; omitting the toxicity term, Eq. (3) was fit to the data. Analogous to curve E of Fig. 1, this represents a classic hormetic response in the absence of toxicity.

D. Data Set 4: Hexachlorobenzene; 0.32–40 ppm; Dietary Admixture; Female Sprague–Dawley Rats

Hexachlorobenzene (HCB), occasionally used in organic synthesis, had at one time been widely used as a fungicide on seed grains. However, between 1955 and 1959, an estimated 3000 cases of porphyria

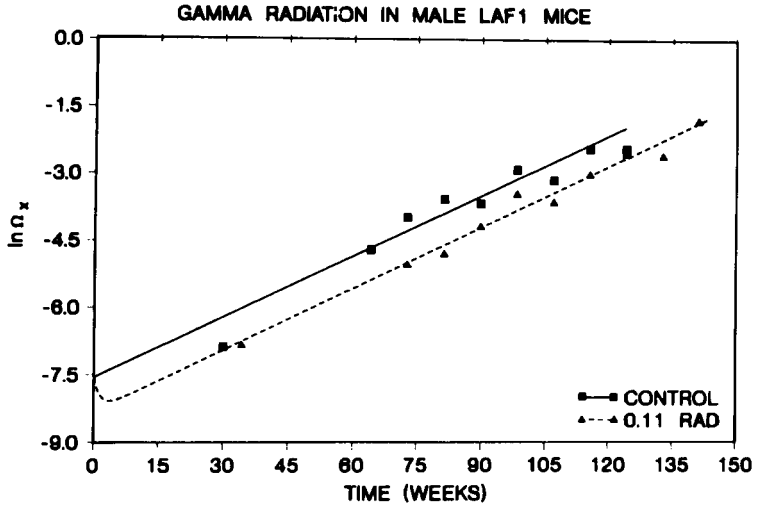

FIG. 12. Gamma-radiation (0.11 rad/day) in male LAF 1 mice: Gompertz plots of Naperian logarithms of age-specific mortality rates versus time for control and treated animals. Gamma-radiation was begun at 1 month of age and continued throughout life (daily doses were administered over 8-h intervals). Time on ordinate refers to that period following initiation of exposure. Parameter estimates and %CV (in parentheses) are: $\ln \Omega_0 = -7.56$ (3.7); $a = 0.0452$ week^{-1} (9.5); $\lambda_D = 0.500$ week^{-1} (963); and $K = 0.659$ week^{-1} (1363). Survival data were obtained from Lorenz et al. [39].

cutanea tarda occurred in Turkey which were traceable to HCB [40]. Apparently, wheat seed sprayed with 10% HCB and intended only for planting, found its way into foodstuffs. It was estimated that patients had ingested approximately 0.05–0.2 g/day for a "relatively long period." Although it is not certain whether HCB per se or its contaminants (polychlorinated dibenzodioxins) were responsible for the lesions [35], HCB use has been markedly reduced since this incident [25].

Figure 13 illustrates Gompertz plots for female control and treated animals. Both hormesis and toxicity are apparent. As with data set 3, the logarithmic-logistic function characterizing hormesis could be simplified by assuming λ_{max} had been reached at the lowest dose (0.32ppm); curve fits were not significantly improved by using the logarithmic-logistic function to characterize hormesis. To improve curve

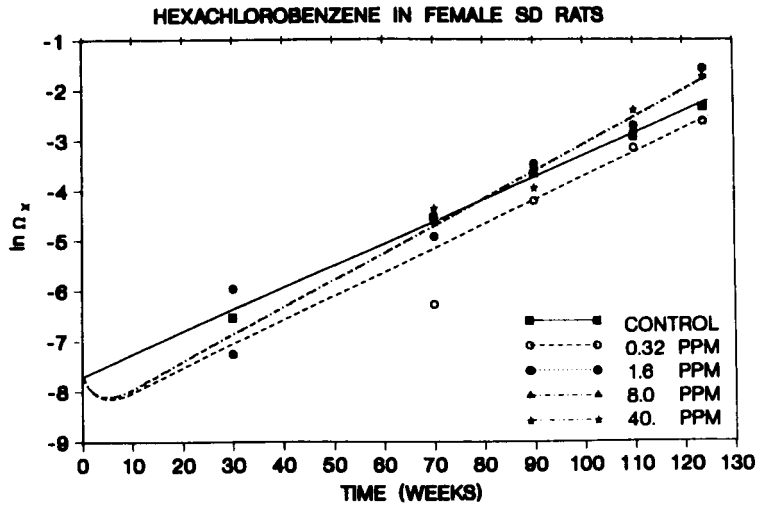

FIG. 13. Hexachlorobenzene (0.32–40 ppm) in female Sprague-Dawley rats (data set 4): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. Hexachlorobenzene feeding was begun at about 30 days of age and continued throughout life. Time on ordinate refers to that period following initiation of exposure. As there are five data points corresponding to each time (30, 70, 90, 110, and 124 weeks), there is some overlap of the points on the graph. Also, the curves corresponding to the three highest dose levels are virtually superimposed on one another (due to saturation of both toxicity and hormesis; see Fig 14). The 30-week time point at the 1.6 ppm dose level was not used in the curve fits (see text). Survival data were obtained from Arnold et al. [25].

fits, a subjective decision was made to eliminate the 1.6 ppm exposed group Gompertzian value at 30 weeks; as this age-specific mortality rate appeared unreasonably high, it was considered an outlier and dropped from least squares analysis. Figure 14 illustrates plots of the hormesis and toxicity indices as a function of dose. As in Fig. 11 (data set 3), the hormesis index maximum was achieved at the lowest dose (*vide supra*). The parameters comprising the toxic term of the logarithmic-logistic function were such that toxicity increased rapidly with dose (this was also apparent with a toxic ED_{50} of 0.36 ppm—see Table 4). Precision, however, is poor for a number of the parameters characterizing hormesis

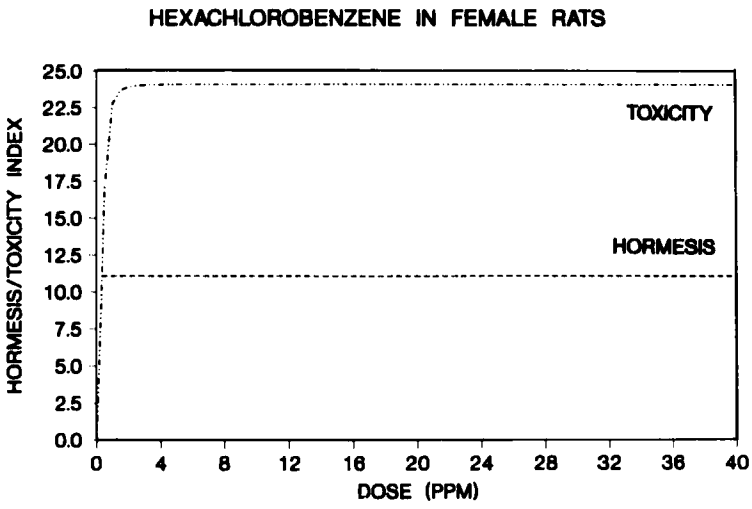

FIG. 14. Hormesis and toxicity indices as a function of dose in female rats (data set 4) receiving hexachlorobenzene in their feed.

and toxicity (see Table 3). Therefore the graphical form taken in Fig. 14 should be viewed more heuristically than definitively. The toxicity index at γ_{max} is only 24 (see Table 5), and median lifespan was never reduced in the 0–40 ppm experimental dose range (see Table 6).

E. Data Set 5: DDT; 2–250 ppm Dietary Admixture; Female CF-1 Mice

DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane], a polychlorinated pesticide, was hailed as the chemical savior of mankind during World War II, and for some time thereafter [41]. By 1962 Rachael Carson [42] was calling it "deadly" and a "poison." Its primary sites of human chronic toxicity appear to be the cerebellum and higher motor cortex [35]. Although some waivers have been granted, DDT has been virtually banned from use in the United States. However, as noted by Coulston [41], the amount of DDT used in the world today (developing countries) rivals the amount previously used in Western nations. In 1984 the World Health Organization and Food and Agricultural Organization of the United Nations established an acceptable intake of 0–0.02 mg/kg/day (this represents a maximum 1.4 mg for a 70-kg man). If we assume that a 70-kg human adult consumes 3 kg of food and liquid per

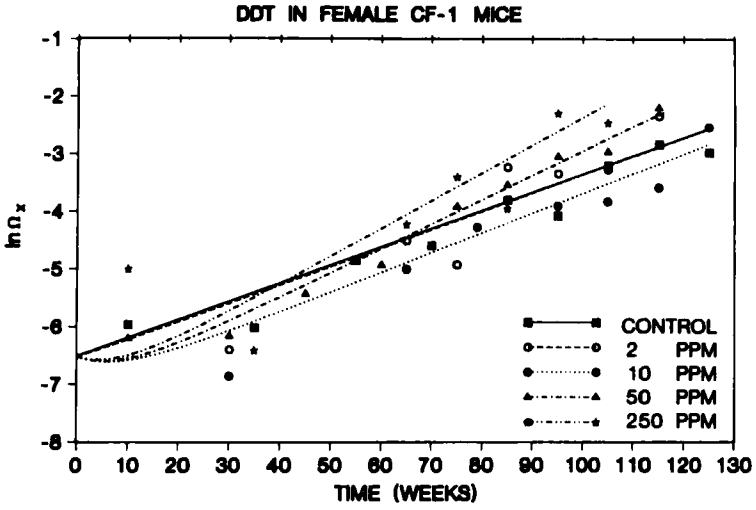

FIG. 15. DDT (2–250 ppm) in female CF-1 mice (data set 5): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. DDT feeding was begun at 6–7 weeks of age and continued throughout life. Time on ordinate refers to that period following initiation of exposure. The 2 ppm curve is virtually superimposed upon that of controls. Survival data were obtained from Tomatis et al. [26].

day, DDT would need to be uniformly present at a concentration of 0.467 ppm to achieve this suggested maximum 0.02 mg/kg/day input. Whereas virtually no one would question the damage DDT has done to the environment and many of its inhabitants, the impact on human health from ingestion of trace amounts of DDT has not been well characterized.

Figure 15 illustrates Gompertz plots from female control and treated mice given food containing various levels of DDT. Both hormesis and toxicity are apparent. Interestingly, Laws [43] reported in 1971 that DDT might have an inhibitory effect on at least one type of experimental cancer.

The logarithmic-logistic function parameters used to characterize hormesis and toxicity are summarized in Table 3. None could be estimated with reasonable precision. ED_{50} values are listed in Table 4; note that the hormetic ED_{50} (4.93 ppm) is about one-seventh the toxicity ED_{50}

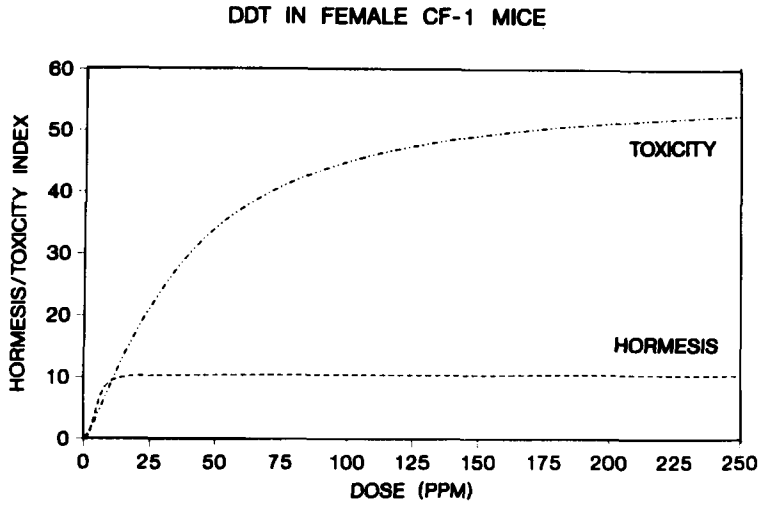

FIG. 16. Hormesis and toxicity indices as a function of dose in female mice (data set 5) receiving DDT in their feed.

(36.4 ppm). This is the primary reason why the maximum hormetic benefit observed experimentally occurred at an intermediate 10 ppm dose (see Fig. 15). The 2 ppm Gompertz function is virtually superimposed onto that of controls. Paradoxically, mice receiving 10 ppm DDT were better off (from a mortality standpoint) than those receiving 2 ppm DDT. This is also confirmed in Table 6, which indicates a 14% increase in median survival time for the 10 ppm DDT group. The threshold dose for a decrease in median survival time is 47 ppm (Table 7).

Figure 16 illustrates the hormesis and toxicity indices as a function of dose. Note that the hormesis index exceeds the toxicity index at low ppm food concentrations. One may also note from Figs. 16 and 17 and Tables 5–7, however, that once DDT exposures began to increase, toxicity dominated.

F. Data Set 6: DDT; 2–250 ppm Dietary Admixture; Male CF-1 Mice

Figure 18 illustrates Gompertz plots from male controls and mice given food containing various levels of DDT. Overall, this data set was similar to that in females (data set 5), except there was no dose level which produced a net hormetic effect over the entire lifespan. Figure 19 shows the hormesis and toxicity indices as a function of dose; unlike the females (Fig. 16), the hormesis index never exceeds the toxicity index.

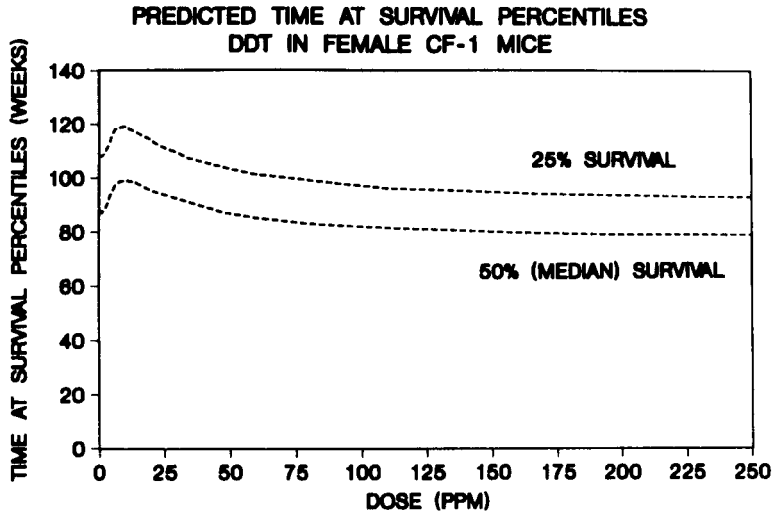

FIG. 17. Median (50%) and 25% survival times for female mice exposed to DDT in feed (data set 5). Notice how survival improved, reached a maximum, and then decayed below that of controls. Curves were generated from theoretically derived parameters.

V. OVERVIEW AND SUMMARY

A Gompertz age-specific mortality rate model for aging, hormesis, and toxicity has been developed and tested. The basic underlying assumptions are: (1) the Napierian logarithm of age-specific mortality rate (Gompertzian) is a linear measure of the mean intensity of physiologic injury for a homogeneous mammalian population maintained in a uniform environment and kept free of preventable disease; (2) aging, hormesis, and toxicity superimpose their injury and age-specific mortality effects independent of one another; (3) with uniform toxicant exposure, nonrepairable increments of toxicity accumulate in an age-independent fashion; (4) with uniform toxicant exposure, hormesis benefit accumulates at a constant age-independent rate but dissipates at a first-order rate; and (5) hormesis and toxicity dose-responses may be characterized by the logarithmic-logistic function. Six experimental data sets employing methylene chloride, gamma-radiation, hexachlorobenzene, and DDT administered to laboratory animals were shown to be consistent with the model. Although characterization of

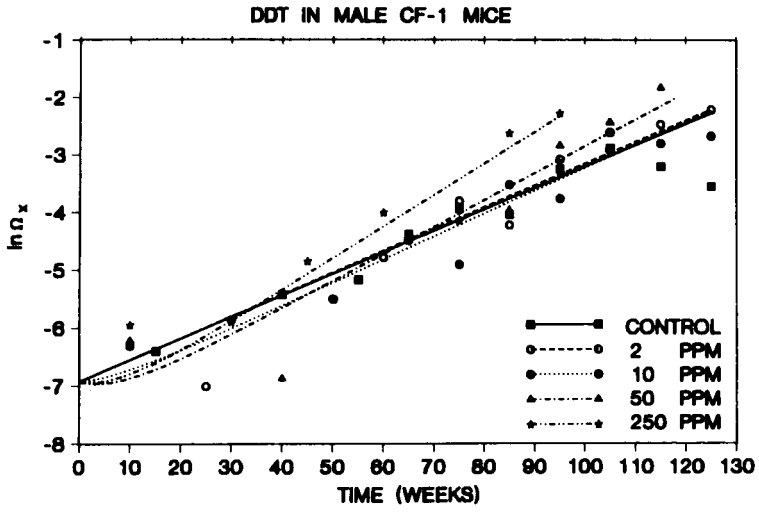

FIG. 18. DDT (2–250 ppm) in male CF-1 mice (data set 6): Gompertz plots of Napierian logarithms of age-specific mortality rates versus time for control and treated animals. DDT feeding was begun at 6–7 weeks of age and continued throughout life. Time on ordinate refers to that period following initiation of exposure. Survival data were obtained from Tomatis et al. [26].

Gompertz functions was generally achievable, precision of logarithmic-logistic function parameter estimates was poor. Therefore, extrapolation of system behavior beyond the experimental dose region is precarious; nonetheless, some extrapolations were made in order to better visualize system properties.

In general, hormetic effects do not approach toxic effects in magnitude of response. Coupled with their reversibility, hormetic benefit can nearly always be nullified by toxicity (e.g., see Fig. 17). Therein lies the danger of speculation about the human situation; although some evidence indicates that low exposures to toxic substances produces net beneficial effects in animals, unless we have extensive experimental data and are capable of extrapolating these data to man, we can never be quite sure how low we need go to get comparable results in man. In fact, the existence of longevity hormesis has not yet unequivocally been established to occur in man.

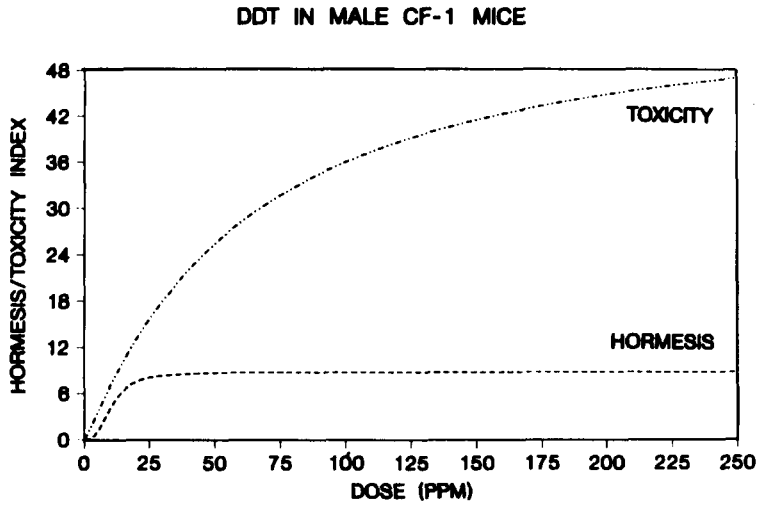

FIG. 19. Hormesis and toxicity indices as a function of dose in male mice (data set 6) receiving DDT in their feed.

In view of an ever-expanding body of knowledge that low dose exposure of laboratory animals to a variety of toxic agents can elicit longevity hormesis (promote health), and that toxicity can mask hormesis at higher doses, the assumption that high-dose chronic toxicity studies per se can generate realistic estimates of health risk at low doses is challenged. Longevity hormesis is a phenomenon that investigators working in the area of risk assessment must contend with in terms of both experimental design and data analysis. Continued denial of its existence is no longer tenable.

Unlike conventional risk assessment paradigms which focus almost exclusively on lifetime cancer risk, age-specific mortality analysis provides an index of injury to all vital system states. Nervous system toxicity, for example, would in all likelihood affect mortality and thus indirectly be detected and quantitated by the methods outlined here. Certainly, the inclusion of age-specific mortality analysis to data obtained from long-term toxicity studies would provide an additional tool with which to confront, identify, and quantitate health hazard.

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