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THRESHOLD AND DOSE RESPONSE ESTIMATION USING THE "FILTER MODEL"

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The "filter model" has been developed to explain the biologic effects of radiation and chemicals. We have examined nearly 300 sets of dose response data, of which 50 are presented here. Responses (induced by radiation and chemicals) which have been examined include *in vitro* survival studies on animal and plant tissues, induction of cellular aberrations and time to tumor or death. Similar data from *in vivo* studies has also been examined. All of the data appear to fit the model $R = a \ln D + b(\ln D)^2 + c$, where R is the response, a and b are parameters fitted by regression to a particular set of data, and c is the response at zero (or lowest) dose. By writing this model in exponential form, it can be seen that the response R results from multistage filtering (by net amounts a and b) of the initial dose, D. The threshold is obtained from this model as the point, $\hat{D}_T$, at which the second derivative becomes zero. This is given by $\hat{D}_T = \exp(1 - a/2b)$ when a and b are oppositely signed.

Introduction

Recent United States federal legislation has brought into sharp public focus questions and scientific controversies about results from studies at high doses which are used for extrapolation to low doses. The models used for extrapolation are highly controversial (Groer *et al.*, 1978; Lewis, 1980), and acceptance of a given result is often based on a legal or nonscientific criterion rather than a technical one. For example, as a result of a law suit brought against the US Environmental Protection Agency (USEPA) by the Natural Resources Defense Council, a public interest group, the US District Court mandated a list of compounds to be studied and regulated by the USEPA. The proposed environmental criterion for carcinogens of an absolute value of zero is based neither on scientific data nor on technological feasibility.

Totter and Finamore (1978) have noted that perhaps because of the controversy

> ...over the proper method of extrapolating to low doses and of comparing the dose-response curves of one species with the curves of other species...the dose-response information that was gradually accumulated was never collected and comprehensively analysed.

These authors began the process of such analysis by comparing the dose–response behavior of 37 data sets

representing a wide range of organisms, exposure mechanisms, and toxicants. For this comparison, they employed a saturation curve [Eq. (1)] suggested earlier by Totter (1974).

$$\log(1/f-1) = -n(\log D - \log K), \qquad (1)$$

where D is the dose in rem, mg/kg, or other appropriate units, K, the dose required to produce a 50% effect, and f, the fraction of subjects affected, are solved for by least squares.

Totter and Finamore's (1978) conclusions that there is no response unique to radiation as distinct from chemicals, that simple models containing a few parameters of which (at least) one is related to the genetic material, and "...an unexpected universality of biological behavior that may be helpful in the extrapolation of experimental data to humans" support the conclusions (Janardan and Schaeffer, 1977) reached earlier. At that time, we had developed as a model of the processes leading to the production of chromosome aberrations [Eq. (2)], the Lagrangian Poisson Distribution (LPD) [Eq. (3)].

A		B	
Chromosomes queued for damage	$\lambda_1 \rightleftharpoons B$	Chromosomes queued for restitution	(2)

Taking λ_1 as the rate of the damage process and B as the rate of the restitution process, the LPD is obtained as

$$f_K = \lambda_1(\lambda_1 + \lambda_2 K)^{K-1}\left[\exp(-\lambda_1 - \lambda_2 K)\right]/K!, \qquad (3)$$

where f_K is the survival fraction at the Kth dose and $\lambda_2 = \lambda_1/B$. The LPD is the same as the simple Poisson when $\lambda_2 = 0$. Based on examination of over 100 data sets representing radiation and chemical damage to plant, animal, and human tissues we concluded from the model alone that

> ...The mechanisms of damage appear to be independent of the nature of the 'insult.' Also, the same results are found for divergent species, which suggests (from the model alone) similarities in mechanisms which may imply similarities in chromosome structure among various organisms (Janardan and Schaeffer, 1977).

These conclusions are supported and extended by the results reported here.

Data and Discussion

Schaeffer *et al.* (1980a) have shown that the LPD can be used to estimate the energy (ΔG_0) required to produce cell damage by noting that λ_2 is the ratio of rates for the induction and restitution processes. Hence, at equilibrium, λ_2 is the thermodynamic equilibrium constant, K_{eq}. Because of the relationship between λ_2 and K_{eq}, the LPD, like Totter and Finamore's (1978) model, provides a superior way of examining dose–response since thermodynamics can be applied in the examination. Although we have formally demonstrated the relationship between λ_2 and K_{eq}, that between λ_2 (or, in general, response) and dose (D) has not been given.

The relationship can be developed empirically by noting that a plot of λ_2 versus the logarithm of the dose is curved (Janardan *et al.*, 1979). By analogy with Cook *et al.* (1969) and Ciecka *et al.* (1979) the relationship is then given by

$$\lambda_2 = a\ln(D+1) + b\left[\ln(D+1)\right]^2, \qquad (4)$$

where a and b are parameters to be estimated for the model.

A biological understanding of this model is developed by writing Eq.(4) [or subsequently Eq. (5)] in exponential form. In this form, the response is exponential [$\exp(-\lambda_2)$] and the dose is a complex exponential function ($D^a D^{-b\ln D}$). This function is interpreted as the net product of a multistage process which "filters" the initial dose by amounts a and b, where a and b are random variables from an unknown distribution. For this reason we call a model of the Eq. (4) form the "filter model." A formal derivation based on the microdosimetric approach to modelling radiation damage given by Kellerer and Rossi (1972) and Kellerer and Brenot (1974) has recently been developed (Schaeffer *et al.*, 1980b).

Since λ_2 measures the extent of reaction prior to equilibrium, and is the equilibrium constant at equilibrium, it can be replaced by other measures of reaction extent, R:

$$R = c + a\ln(D+1) + b\left[\ln(D+1)\right]^2, \qquad (5)$$

where c is usually taken as the response at zero (or lowest) dose.

Equation (5) is similar to a time to death model [Eq. (6)] used by Cook *et al.* (1969) in which the incidence at time t, I_t, is given by

$$\log(I_t) = C + k\left[\log(t)\right] + d\left[\log(t)\right]^2. \qquad (6)$$

Equation (5), however, expresses the relationship between a generalized dose, D, and a response, R, which is measured on a linear (rather than logarithmic) scale.

Threshold Estimation

The threshold for a dose effect on survival is the point at which the slope between zero dose to the point in question changes, e.g., from positive or zero to negative. The point of slope change for Eq. (5), $\hat{D}_T$, is

Table 1. Dose-survival curves for Totter and Finamore's (1978) chemical agents using Eq. (5).[a]

Substance tested	Response[b]	D[c]	a	b	$\hat{D}_T$	R^2	Reference[a]
Dibenzanthracene	Sub Q tumor	mg/Kg	−0.8660	0.1875	0.15	0.97	Bryan (1943)
Dibenzanthracene	Sub Q fibrosarcoma	mg/Kg	−0.4151	0.06748	0.15	0.98	O'Gara (1965)
Dimethylbenz(*a*)anthracene	mammary tumor	mg/Kg	0.1547	−0.0644	9.04	0.97	Philips (1973)
Benzo(*a*)pyrene	respiratory tract tumor	mg/Kg	0.2230	−0.0587	18.19	0.96	Peron (1973)
Benzo(*a*)pyrene	papilloma	mg/Kg	0.0508	−0.02488	7.54	0.996	Poel (1959)
Dibenzpyrene	Sub Q fibrosarcoma	mg/Kg	0.06096	−0.1654	3.27	0.99	Wodinsky (1965) (16 week)
Diethylstilbesterol	mammary carcinoma	mg/Kg	0.04840	−0.01603	12.30	0.95	Gass (1964)
Urethane	tumors	mg/Kg	−0.0570	−0.00338	0.20[d]	0.996	Schmahl (1977)
Urethane	tumors	mg/Kg	−0.1826	0.2296	0.10[d]	0.997	Schmahl (1977)
Aflatoxin B_1	carcinomas	mg/Kg	0.1561	−0.0788	7.32	0.98	Wogan (1974)
Vitamin D	bone ash increase	e	0.1188	−0.08025	5.70 (4.75)[d]	0.989	Waddell (1947)
4-Dimethylethyl-aminoazobenzol	liver tumor	mg/Kg	0.3601	−0.05142	90.22	0.97	Druckrey (1967)
Methylcholanthene	Sub Q tumor	mg/Kg	−0.4769	0.02024	0.29	0.98	Bryan (1943)
Ethylnitrosourea	offspring nervous system tumors	mg/Kg	−0.02881	−0.01582	4.7[d]	0.95	Druckrey (1969)

[a]Data from Tables 1 and 2 of Totter and Finamore (1978) which should be consulted for the original references.
[b]Response scored as surviving fraction at a given dosage and corrected for survival fraction at lowest dose. All data points used unless otherwise specified.
[c]Dosages correspond to those given in "Calculated Dosage" columns of Totter and Finamore (1978).
[d]Threshold calculated using the procedure in Schaeffer *et al.* (1980c).
[e]Dose in units per 100 g of feed.

d by setting the second derivative equal to zero. gives

$$\hat{D}_T = \exp(1 - a/2b). \qquad (7)$$

: change occurs if either a or b is negative. If both the same sign the slope cannot change and the hold cannot be calculated in this fashion and the :dure given in Schaeffer *et al.* (1980c) must be (Table 1). The use of Eq. (5) and Eq. (7) to ate the threshold is most readily discussed in on to radiation experiments.

:diation is highly penetrating, and because of this threshold for radiation damage exists it should · at about the same level in *in vivo* and *in vitro* ns. The experiments in Tables 2 and 3 were con- d over doses of several hundred to tens of thou- of rads. The $\hat{D}_T$ values determined for these data a geometric mean and 95% confidence limits of $24.18 < 35.63$. An additional 80 sets of radiation not included here afforded $\hat{D}_T$ values between 5 0 rads. This range is less than 1% of the range of mmon experients (those with high doses < 5,000 In Conger and Constantin's (1974) experiment rley seeds the lowest dose was 8700 rads. How- the estimated threshold (272 rads) is reasonably to the values given in Table 2. Whether the nce is real and reflects some differences in the ses of animals and plants, or comes from having olated nearly 9000 rads (between zero and the measured dose), cannot be ascertained with cer- from our results. However, comparison with Smith *et al.*'s (1974) data on the effects of X-rays on maize seeds in which the low dose was 0.5 rads and $\hat{D}_T = 4.2$ rads, and with Bauer and Kaufman's (1938) study of Drosophila sperm where the low dose was 1000 rads and $\hat{D}_T = 95$ rads, suggests that the high $\hat{D}_T$ value found for Conger and Constantin's (1974) data is from extrapolation over a large range rather than from biologically related response differences between plants and animals. This example illustrates the extremely high predictive power of Eq. (5) to model d e- response effects over the studied range since a 9000 rad extrapolation affords a predicted threshold within a factor of 3 of the other estimates. The ability to use the model to reasonably estimate a threshold from high dose data is of particular importance in assessing the health significance of low doses of environmental mutagens carcinogens, or radiation (Groer *et al.*, 1978; Lewis, 1980).

In order to facilitate comparisons between models, Tables 1 and 2 summarize the results obtained from Eq. (5) using the data in Totter and Finamore's (1978) Tables 1 and 2. In our work, the responses are the fraction surviving the exposure. In Tables 1–3, c is taken as the survival at lowest dose. Other choices of c, such as $c = 1$ when the response is survival fraction, or $c = 0$ when scoring chromosome breaks only slightly affects most of the models. Thus, for Druckrey *et al.*'s (1969) study on the production of neuroepithelial tumors in the offspring of pregnant female BDIX rats exposed to ethylnitrosourea, the observed survivals are 0.4, 0.22, 0.10, 0.03, 0.02, while the survival fractions predicted from Eq. (5) with $c = 0.4$ and $c = 1.0$ are 0.30,

Table 3. Continued.

Substance tested/system	Dosage	Survival	Estimated[a] survival	R^2	$\hat{D}_T$	Investigator
X-rays	400 R	0.500	0.53	0.99	55.9	Badr and Badr (1971)
survival fraction of	600	0.368	0.31			
Rattus rattus	800	0.130	0.147			
15 days	1000	0	0.01			
X-rays	400 R	13.8	14.1	0.97	56.9	Badr and Badr (1971)
mean survival (days) for	600	11.7	11.6			
30 day decedents	800	10.6	9.6			
Rattus rattus	1000	7.2	7.9			
^{60}Co γ-rays	25 R	0.96	0.990	0.90	18.5	Newcombe and
fraction without	50	0.975	0.978			McGregor (1975)
gross body malformations	100	0.969	0.961			(experiment 1)
from irradiation of	200	0.960	0.941			
trout sperm	400	0.902	0.917			
^{60}Co γ-rays	25 R	0.992	1.000	0.81	21.4	Newcombe and
fraction without	50	0.994	0.994			McGregor (1975)
gross body malformation	100	0.990	0.986			(experiment 4)
from irradiation of	200	0.987	0.975			
trout sperm	400	0.953	0.962			
Average latency period	50 ppm	135	109.9	0.94	28.9[b]	Maltoni (1977)
(weeks): angiosarcoma	250	79	97.1			Table 8
in Sprague-Dawley rats	500	81	91.1			
exposed to vinyl chloride	2500	78	75.9			
	6000	70	67.0			
	10000	64	61.6			
Fraction of Sprague-Dawley	50 ppm	0.98	0.95	0.91	3.3	Maltoni (1977)
rats without angiosarcoma	250	0.93	0.91			Table 8
after vinyl chloride	500	0.88	0.89			
exposure	2500	0.78	0.84			
	6000	0.78	0.81			
	10000	0.85	0.79			
Average latency period	50 ppm	51	48.4	0.96	3.0	Maltoni (1977)
(weeks): lung tumors in	250	45	45.8			Table 17
Swiss mice exposed to	500	41	44.4			
vinyl chloride	2500	43	40.5			
	6000	38	38.0			
	10000	36	36.4			
Fraction of Swiss mice	50 ppm	0.965	0.70	0.93	29.1[b]	Maltoni (1977)
without lung tumors	250	0.43	0.57			Table 17
after vinyl chloride	500	0.34	0.52			
exposure	2500	0.43	0.38			
	6000	0.3	0.30			
	10000	0.3	0.25			
Fraction of *Calandra*	1.08 ppm	1	0.96	0.96	1.28[b]	I. R. Bursine as
granaria surviving	1.47	0.68	0.71			given in Finney (1971)
ethylene oxide	1.58	0.43	0.63			Table 4.4
exposure	1.68	0.61	0.56			
	1.82	0.74	0.46			
	2.06	0.12	0.28			
	2.10	0.27	0.25			
	2.30	0.06	0.09			
	2.46	0	0.00			

[a]Corrected for survival at lowest dose.
[b]Threshold calculated using the procedure in Schaeffer *et al.* (1980c).

).17, 0.07, 0.00 ($R^2=0.95$, $\hat{D}_T=4.74$ mg/kg), and 0.23, 0.12, 0.04, 0.007 ($R^2=0.9996$, $\hat{D}_T=0.06$).

le 3 presents several data sets not reported by and Finamore (1978). The examples include on survival after irradiation or exposure to als. Additional examples use time to death as the response. Although for the latter we use c as the survival time at the lowest dose, it might be desirable to treat c as a parameter to be fitted if the data set is large enough. If c is treated as a parameter, then its value is an estimate of the survival time at zero dose. For the Swiss mice developing lung cancer after exposure to vinyl chloride [Maltoni's (1977) data given in Table 3].

the estimated survival time at zero dose is 67 weeks, for example. [The reader should be aware that Peto (Federal Register, 1980) has suggested that there may be no real time-to-tumor dose response effect, and that the interpretation of such data may be more complex.]

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An analytical scheme was developed for vinyl chloride, which is applicable to ambient and in-plant atmospheres. Using computerized gas chromatographs equipped with automatic injection system and flow rate control, high reproducibilities are achieved in the ppb range. Samples from various sources have been analyzed.

Improved methods for sampling and analysis of vinyl chloride

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Introduction

Because of increased public health and environmental concern about the effects of vinyl chloride on human health.[1-3] Regulations have been promulgated by several countries, ordering reduction in the concentrations which had been present in industrial and ambient urban atmospheres prior to such promulgation.[4] Compliance with these various regulations demands straightforward, reliable analytical methods, which can be applied to a broad range of air concentrations and sampling techniques. In addition, unit analytical time should be very short because of the large number of samples which have to be processed. Gas chromatography, because of its fast turn around time, wide concentration linearity and high sensitivity for lightweight hydrocarbon molecules, has been selected as the analytical finish for a variety of sample types, including air, water, polymer resins, and solid polymer stocks, filled or unfilled, plasticized or unplasticized.[5]

Current processes for the production of vinyl chloride monomer (VCM) fall into one of the following classes.[6]

(1) The direct chlorination of ethylene with subsequent dihydrochlorination.
(2) The addition reaction of acetylene and hydrochloric acid.
(3) A combination of direct and oxychlorination of ethylene with subsequent dihydrochlorination.

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