Quantitative Risk Assessment

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This paper presents a brief survey of current methodology available for quantitative risk assessment of environmental carcinogens. Four current models for low-dose extrapolation are reviewed. Current problems and controversies and possible options in doing quantitative risk assessments based on chronic animal studies are discussed.

Reducing the mortality and morbidity of cancer in the United States has become an important regulatory problem. To date, approximately 26 chemicals have been shown to be carcinogenic in man. Many other chemicals have shown mutagenic and carcinogenic potential in animals and are considered to be possible human carcinogens. Most of these chemicals either cannot be entirely removed from the environment or can be removed only at enormous expense. Their environmental presence creates an urgent need for a methodology to assess the risk to man associated with various exposure levels. Such methodology is often referred to as quantitative risk assessment.

Quantitative risk assessment is defined as the estimation of levels of exposure to a toxic substance which lead to specified increases in lifetime incidence rates or in the probable occurrence of a given undesirable consequence. For example, the primary topic of discussion concerns a lifetime carcinogenic risk of, e.g., 10^{-6} from a given daily exposure to a particular carcinogen. This lifetime risk will be for the "average" person in the United States. Often, such risk estimates do not apply to particular susceptible subgroups of the population which are more highly exposed than the average, or more prone to cancer because of other high-risk factors, or at higher-risk levels because of additional exposures to other carcinogens. Any such quantitatively arrived at risk assessment must be interpreted carefully.

One question which immediately arises is "Why should one try to quantify exposure levels leading to very small lifetime risks?" Such attempts at quantification are becoming increasingly important as a result of the refined capability of detecting environmental toxic pollutants and of recognition of the mutagenic and carcinogenic potential of a larger number of substances. Regulation of exposure is required by the following government agencies: the EPA — under acts such as the Drinking Water Act and the Toxic Substances Control Act (TSCA); the Food and Drug Administration — in setting tolerance levels of pesticide residues; the Consumer Product Safety Commission — for regulating consumer products; and the Occupational Safety and Health Administration — for regulation of the workplace environment. Requirements for regulated exposure have been amply demonstrated in a recent report of the Interagency Regulatory Liaison Group (IRLG, 1979).[1] Regulation of substances such as aflatoxin, vinyl chloride, DDT and benzene is rarely a simple question of banning or not banning; rather, it is a matter of regulating exposure levels to prevent undue hazard. For this, estimates of additional risk due to a given exposure are required.

For making such risk estimates there are generally three sources of data: epidemiologic data, short-term mutagenic assays, and chronic animal studies. Each of these sources of data has its limitations for risk assessment. Epidemiologic data is superb for risk assessment for man when good data is available. However, such data is usually unavailable for new substances, and for existing substances it is often difficult and expensive to gather. Furthermore, even when data has been gathered for a chronic exposure it is hard to determine retrospectively the average daily exposure of any individual. It is extremely difficult to separate the effects of confounding factors, e.g., exposure to other carcinogens and life-style risk factors, from the lifetime effect of a low-level repeated exposure to the single substance under study.

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Table 1. — Quantal Response Data from an Animal Study.

Dose Level	$d_0 = 0^*$	d_1	d_2	...	d_m
Number of animals tested	n_0	n_1	n_2		n_m
Number of animals with toxic response	x_0	x_1	x_2	...	x_m

*$0 = d_0 < d_1 < d_2 < \ldots < d_m$

Epidemiologic data, when available, should be used to supplement, support or modify the results of animal studies.

Although the rapidly developing use of short-term mutagenic testing offers immense promise, such assays are currently quite limited for quantitative risk estimation for man. They are helpful in identifying possible carcinogens and in relating possible potencies of carcinogens. They also are extremely useful in determining priorities for further expensive chronic testing. However, the main basis for quantitative risk assessment is still the chronic animal study.

Risk Assessment from Animal Chronic Studies

The typical animal chronic bioassay is carried out with groups of animals given lifetime exposure to the toxic substance at fixed dose levels. At the end of the study, the number of animals showing toxic response of interest (e.g., tumor, death) is recorded. The type of data obtained from such an experiment is shown in Table 1.

In Table 1, the dose level $d_0 = 0$ represents the control group for the study and the other dose levels are at increasing levels. Table 2 shows, as an example, data obtained from a chronic study in rats[2] in which the response was the occurrence of liver tumor based on exposure to dimethylnitrosamine (DMN).

How to use such data to make a risk assessment for man involves two fundamental problems. The first problem is extrapolation of the data from the relatively high-dose levels of exposure of the animals to the low levels corresponding to a small prescribed risk level, i.e., 10^{-5} or 10^{-6}. This is the so-called *low-dose extrapolation problem.* It is primarily a statistical problem and will be discussed later in this paper. The second problem, the *species conversion problem,* is that of converting the dose level for the species under test (e.g., the rat in Table 2) to that for man. The method of conversion is based sometimes on surface area and sometimes on a daily dietary body-weight (mg/kg/day). The method of choice depends on how the body handles the toxic substance in question.

Table 2. — Data for Dimethylnitrosamine.

Dose Level (ppm)	0	2	5	10	20	50
Number of test animals	29	18	62	5	23	12
Number of responses	0	0	4	2	15	10

Relevant considerations are the similarity of metabolism between species, route of exposure and other such factors. They are discussed in the DHEW report of Hoel et al.,[3] the Report of the Scientific Committee of the Food Safety Council,[4] and the National Academy of Science report on *Drinking Water and Health.*[5]

Dose-Response Models. — The well-known concept of a dose-response function is employed in discussing the methodology of low-dose extrapolation. Such a function is given by P(d) which represents the probability that an animal on chronic test at dose level d will show the toxic response under study. Assuming there are no background response rate and no threshold, such a model would have $P(0) = 0$ and $P(d) > 0$ for $d > 0$ and would increase as the dose d increases. A typical dose-response function is shown in Fig 1.

Various dose-response models have been proposed in the literature. Four such models are presented in this study: the one-hit model and three generalizations of the one-hit model — the multistage model, the multihit model and the Weibull model. Their equations are given in Table 3.

There exists a plausible biological basis for each of these models and it is not clear which, if any, of these models is appropriate for any particular suspect carcinogen. For a discussion of the one-hit model see Hoel et al[3] and the BEIR report (1972). For a discussion of the multistage model see Crump et al[6] and Crump, Guess and Deal.[7] The multihit model was derived by Cornfield[8] and Rai and Van Ryzin.[9] Finally, the Weibull model was derived from a variety of biological model considerations. Such reasoning includes a multistage modeling as in Armitage and Doll[10] in which lifetime incidence rate for single cell alteration in each stage is proportional to d alone, a multihit modeling as in Nordling[11] or a one-hit model where the governing lifetime incidence rate for a single hit is proportional to d^m for any $m > 0$.

Note that each of the three models given by Equations (2), (3) and (4) is a generalization of the one-hit model of Equation (1). For themultistage model with $k = 1$ and $\alpha_1 = \beta$, Equation (2) becomes Equation (1). Also, Equations (3) and (4) for the gamma and Weibull multihit

Table 3. — Four Dose-Response Models.

Model	P(d) = Probability of a Test Animal Responding at Dose Level d	Parameters of the Model	Eq. No.
One-hit	$1 - \exp(-\beta d)$	$\beta > 0$	(1)
Multistage	$1 - \exp\{-(\alpha_1 d + \alpha_2 d^2 + \ldots + \alpha_k d^k)\}$	k, an integer $\alpha_i \geq 0, i = 1, \ldots, k$	(2)
Multihit	$\int_0^{\beta d} \{u^{k-1}\exp(-u)/\gamma(k)\}du.$ $\gamma(k) = \int_0^{\infty}\{u^{k-1}\exp(-u)\}du$	$k > 0$ $\beta > 0$	(3)
Weibull	$1 - \exp(-\beta d^m)$	$m > 0$ $\beta > 0$	(4)

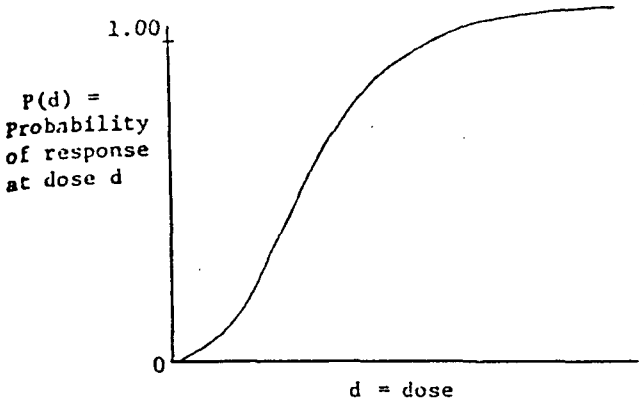

Fig 1. — A dose-response curve.

models reduce to Equation (1) if k = 1 and m = 1, respectively.

For each of the models in Table 3 one can incorporate a background response rate by the use of Abbott's[12] correction. The extended model with background now becomes:

$$P^*(d) = p + (1-p)P(d) \qquad (5)$$

where P(d) is one of the models in Table 3. From the point of view of quantitative risk assessment the problem is to consider either the quantity P*(d) - P*(0) or the quantity P(d) = (P*(d)-P*(0))/(1-P*(0)). These two quantities without background, p = P*(0) = 0, are identical. Either quantity represents an *increased risk over background due to the added dose d.* Setting such increased risk to an arbitrarily chosen small risk level P_0, usually in the range of $P_0 = 10^{-4}$ to $P_0 = 10^{-6}$, one obtains the dose level d_0 which corresponds to an increased risk of P_0. Such a dose level is referred to as the virtual safe dose (VSD). For example, if $P_0 = 10^{-6}$ represents a lifetime risk of liver cancer due to daily DDT exposure in the drinking water, then the VSD d_0 is that daily dose level leading to this increased risk for the species on test. Converting that dose to man would give him the equivalent daily dose which would cause approximately three additional liver cancers per year in the U.S. This calculation is based on approximately 220 million people in the U.S. with an average lifetime of 73 years; this would lead to N = 220/73 = 3,000,000 people at risk per year — hence $NP_0 = (3{,}000{,}000) \times 10^{-6} = 3$ additional liver cancers per year to DDT in the drinking water. Obviously, such a calculation is over-simplified and refers to only the "average" person, not the person consuming more water or subject to other DDT contamination. Such calculations are useful, however, for quantifying additional cancer cases due to given exposure levels.

Low-Dose Extrapolation. — Using any one of the mathematical models from Table 3, one can now carry out the low-dose extrapolation as follows. From the data in Table 1, assuming one has randomly assigned the animals to the various dose groups and has held all factors between animal groups under control with only the dose levels varying, one can write down the probability of obtaining the results from the experiment in Table 1 as:

$$\prod_{i=0}^{m} \binom{n_i}{x_i} (P^*(d_i))^{x_i} (1-P^*(d_i))^{n_i-x_i}, \qquad (6)$$

where P*(d) is as in equation (5) and $\binom{n_i}{x_i}$ is the usual combination of n_i objects taken x_i at a time. Equation (6) is arrived at by the usual binomial response arguments and from it one can use statistical procedures to estimate the parameters of the model under consideration and use these estimates to form an estimate of the function P(d) denoted by $\hat{P}(d)$. Typically, $\hat{P}(d)$ will be P(d) with the estimated parameter values replacing the true parameter values. Solving the equation $P_0 = \hat{P}(\hat{d}_0)$ for $\hat{d}_0$ one then obtains an estimate $\hat{d}_0$ of the virtual safe dose at the preassigned increased risk level of P_0. The methodology for doing this is not detailed here. It can be found for the one-hit model in Hoel et al,[3] for the multistage model by Crump, Guess and Deal,[7] for the gamma multihit model by Rai and Van Ryzin,[9,13] and for the Weibull multihit model by using a nonlinear maximum likelihood estimation technique as in a 1980 revision of the *Report of the Scientific Committee of the Food Safety Council.* The results in the next section when using the Weibull model have been furnished to the author by Frank Carlborg and use nonlinear weighted least squares estimation.

Applications to Three Data Sets

Methodologies will be applied to each of three data sets to illustrate the use of the methodologies previously cited. The first data set is presented in Table 2; and Tables 4 and 5 give the other two data sets. Table 4 gives the data of a chronic study on DDT by Tomatis et al[14] and is for mice which developed liver hepatoma. Table 5 gives the data of a chronic study on ethylene thiourea by Graham et al[15] and pertains to rats which responded with thyroid carcinoma.

The results for the four models for the three data sets of Tables 2, 4 and 5 are shown in Tables 6, 7 and 8, respectively. The estimate for the background parameter p is also given in each case.

Some immediate conclusions seem apparent in studying Tables 6 to 8. In every case the smallest estimate of VSD was given by the one-hit model, the second smallest by the multistage, the second largest by the Weibull and the largest by the multihit. This ordering is not unique with these three data sets. In fact, typically when $\hat{k}$ and $\hat{m}$ are greater than one, this will be the case. The reason for this is that the multistage, multihit and Weibull models

Table 4. — Data for DDT.

Dose Level (ppm)	0	2	10	50	250
Number of test animals	111	105	124	104	90
Number of responses	4	4	11	13	60

Table 5. — Data for Ethylene Thiourea.

Dose Level (ppm)	0	5	25	125	250	500
Number of test animals	72	75	73	73	69	70
Number of responses	2	2	1	2	16	62

Table 6. — Results for Dimethylnitrosamine.

Model	Estimates of Parameters	Estimates of VSD in ppm at Risk Level 10^{-4}	10^{-6}	10^{-8}
One-hit	$\hat{p} = 0$			
Eq. (1)	$\hat{\beta} = 0.03249$	3.1×10^{-3}	3.1×10^{-5}	3.1×10^{-7}
Multistage	$\hat{k} = 3, \hat{p} = 0$			
Eq. (2)	$\hat{a}_1 = 0.01766$	5.7×10^{-3}	5.7×10^{-5}	5.7×10^{-7}
	$\hat{a}_2 = 0.000728$			
Multihit	$\hat{p} = 0$			
Eq. (3)	$\hat{\beta} = 0.08538$	1.3×10^{-1}	1.2×10^{-2}	1.0×10^{-3}
	$\hat{k} = 1.91$			
Weibull	$\hat{p} = 0$			
Eq. (4)	$\hat{\beta} = 0.00828$	4.6×10^{-2}	1.8×10^{-3}	7.3×10^{-5}
	$\hat{m} = 1.43$			

are all responding to the nonlinearity in the data in the observed dose range and compensate for this by higher-order terms in the multistage model and by powers of dose in the other two models. For a fuller discussion of this phenomena with the multihit model see Rai and Van Ryzin. More comparisons of the four models illustrating this phenomenon will appear in a 1980 revision of the *Report of the Scientific Committee of the Food Safety Council.*

Although examples are not given here, the exact opposite is true if $\hat{k}$ and $\hat{m}$ are less than one in the multihit and Weibull models, respectively. In such cases the ordering of the VSD estimates from largest to smallest will be one-hit, multistage, Weibull and multihit. Thus, the one-hit model is the least sensitive to data nonlinearities, the multistage the second least, the Weibull the second most and the multihit the most. Implications of these results for low-dose extrapolation will be discussed further in the next section.

In Tables 6 and 7 the answers for the one-hit and multistage models agree in order of magnitude for 10^{-4} through 10^{-8}. This is because the estimate $a_1 > 0$ leads to a low-dose linear term, since Equation (2) has a low-dose behavior which is closely approximated by the polynomial $a_1 d + a_2 d^2 + \ldots + a_k d^k$. In the low-dose range where d is less than 10^{-2}, the multistage model for these two examples is virtually a linear model. This explains the linear behavior of the VSD estimates in Tables 6 and 7, in which one should note that the VSD estimates from the multihit and Weibull models are an order of magnitude larger at risk level 10^{-4} and two to three orders of magnitude larger at 10^{-8}. The reason is that in the low-dose range the multihit and Weibull models do not have a linear term and behave approximately as $c_1 d^{\hat{k}}$ and $c_2 d^{\hat{m}}$ respectively, $c_1 > 0$ and $c_2 > 0$.

Examining Table 8 in which $a_1 = a_2 = 0$ for the multistage, $\hat{k} = 8.23$ for the multihit and $\hat{m} = 3.33$ for the Weibull, a high degree of nonlinear behavior in the dose range can be seen. Thus, the VSD estimates arrived at in Table 8 are from two orders of magnitude larger at 10^{-4} to six orders of magnitude larger at 10^{-8} than those of the one-hit model. However, there is quite good agreement between the three nonlinear models in this highly nonlinear situation.

Issues in Low-Dose Extrapolation

The three examples given previously illustrate the variety of answers one can obtain from low-dose extrapolations by various models. The answers are highly model-dependent and there are questions regarding their validity. Some argue that low-dose linearity is to be expected for all carcinogens because of dose-wise additivity of a postulated background "effective" dose and the administered dose, e.g., Peto[16] and Crump et al.[6] Their argument rests heavily on the dose-wise additivity assumption and a formal mathematical argument using a Taylor series expansion around a linear term with the assumption that the dose-response curve has a *strictly positive slope* at the postulated background effective dose level. Unfortunately the assumptions of dose-wise additivity, an effective background dose and the point that the dose-response curve has a strictly positive slope for all $d > 0$ and all carcinogenic dose-response curves are far from being biologically verified facts. If DNA repair mechanisms are at work, the slope of the dose-response curve may be zero to some point d^* above the

Table 7. — Results for DDT.

Model	Estimates of Parameters	Estimates of VSD in ppm at Risk Level 10^{-4}	10^{-6}	10^{-8}
One-hit	$\hat{p} = 0.035$			
Eq. (1)	$\hat{\beta} = 0.00375$	2.7×10^{-2}	2.7×10^{-4}	2.7×10^{-6}
Multistage	$\hat{p} = 0.045, \hat{k} = 2$			
Eq. (2)	$\hat{a}_1 = 0.00163$	6.4×10^{-2}	6.4×10^{-4}	6.4×10^{-6}
	$\hat{a}_2 = 0.0000102$			
Multihit	$\hat{p} = 0.050$			
Eq. (3)	$\hat{\beta} = 0.0073$	7.6×10^{-1}	4.9×10^{-2}	3.2×10^{-3}
	$\hat{k} = 1.68$			
Weibull	$\hat{p} = 0.044$			
Eq. (4)	$\hat{\beta} = 0.000348$	4.4×10^{-1}	1.8×10^{-2}	7.6×10^{-4}
	$\hat{m} = 1.58$			

Table 8. — Results for Ethylene Thiourea.

Model	Estimates of Parameters	Estimates of VSD in ppm at Risk Level 10^{-4}	10^{-6}	10^{-8}
One-hit	$\hat{p} = 0.012$			
Eq. (1)	$\hat{\beta} = 0.00185$	5.4×10^{-2}	5.4×10^{-4}	5.4×10^{-6}
Multistage	$\hat{p} = 0.022$			
Eq. (2)	$\hat{k} = 4.\hat{a}_1 = \hat{a}_2 = 0$	20.8	4.5	1.2
	$\hat{a}_3 = 1.1 \times 10^{-8}$			
	$\hat{a}_4 = 1.28 \times 10^{-11}$			
Multihit	$\hat{p} = 0.022$			
Eq. (3)	$\hat{\beta} = 0.0235$	60.0	33.5	18.4
	$\hat{k} = 8.23$			
Weibull	$\hat{p} = 0.018$		—	
Eq. (4)	$\hat{\beta} = 2.25 \times 10^{-9}$	25.0	6.3	1.6
	$\hat{m} = 3.33$			

postulated background dose. If dose-wise additivity with the background dose does not hold throughout the dose-range, low-dose linearity may not result. For a further discussion on some of these issues see Cornfield et al.[17]

It appears that the question is not so much whether or not there is necessarily a linear behavior for all carcinogenic dose-response curves at low doses, but whether or not one can rule out such a low-dose possibility based on relatively high-dose experiments. Nonlinearity in the high-dose range and the lack-of-fit of the one-hit (linear) model for a variety of data sets, including the ethylene thiourea data of Table 8, are easy to show. Therefore, the use of models such as the multistage, the multihit and the Weibull, all of which are more flexible for fitting the data in the observed dose range and which include the one-hit model as a special case, seems preferable to use of the one-hit model.

The real problem is how much reliance on any of these models outside the experimental range one should allow. There are those who go to the extreme of blind use of the one-hit model regardless of what the experimental results show in the dose-range studied. Such a procedure was recently recommended by the EPA in the Federal Register for the Water Quality Criteria.[18] Use of the one-hit model is defended partly on the grounds that it is always conservative, is justified by epidemiology and reflects the biological basis of a one-hit mechanism. None of these statements is scientifically completely defensible, but it would appear that use of any of the other three models discussed in Section 2 is preferable to use of the one-hit model. The other models include the one-hit model as a special case and are more flexible for fitting data. If one seeks to protect the public health — a very justifiable goal — one should do so by making more realistic use of the data in order to arrive at more believable estimates. A variety of methods could be adopted which do not rule out low-dose linearity and yet use the experimental data to exploit the shape of the dose-response curve. Crump et al have detailed such a procedure for the multistage model. For the multihit model Van Ryzin and Rai[19] have described a method wherein they give "conservative" confidence limits on the estimates by forcing the k of the model to be as close to one as possible while remaining consistent with the data.

A third method, which could be used with any model, seems worthy of more study. In this method one would use all the data from Table 1 for estimating the parameters of the model; then extrapolate fully with the model to risk levels of 10^{-2} to 10^{-4}, for instance; and then extrapolate further by a linear extrapolation. To illustrate this procedure, the case of the ethylene thiourea data is cited in Table 5 and the results in Table 8. Extrapolating to 10^{-4} yields 20.8, 60.0 and 25.0 as the VSDs with the multistage, multihit and Weibull, respectively. Linear extrapolation from this risk level of 10^{-4} to 10^{-6} would merely result in the division of each of the VSDs by 10,000 to obtain 2.1×10^{-3}, 6.0×10^{-3} and 2.5×10^{-3} as the VSDs for the prescribed risk level of 10^{-6}. These results are fully three orders of magnitude larger than that of 5.4×10^{-6} predicted by the super-conservative one-hit model. Admittedly, the example chosen here has a steep dose-response curve ($\hat{m} = 3.33$ for the Weibull, $\hat{k} = 8.23$ for the multihit and $a_1 = a_2 = 0$ for the multistage). This was chosen to emphasize how methods allowing for low-dose linearity in extrapolation may give answers quite different (by three orders of magnitude) from those obtained from blind use of the one-hit (linear) model. In the examples of Tables 6 and 7 use of the multihit and the Weibull models would result in answers differing by roughly one order of magnitude from the answer obtained by use of the one-hit model; use of the multistage model would produce a result differing by only a factor of two from that obtained by use of the one-hit model.

Summary

The use of a variety of models to get answers in or near the experimental range is advocated, followed by linear extrapolation based on other judgements. How conservative one wishes to be in the extrapolation should be determined by public health, biological, economic and other concerns and not by automatic choice of the one-hit model when it does not fit the data. It is hoped that some of these issues can be developed in more detail in future papers. The purpose of this paper was merely to review some of the available recently developed models for low-dose extrapolation and to show how they behave when applied to data. For a further illustration of this on more data sets see the 1980 revision of the *Report of the Scientific Committee of the Food Safety Council.*

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Threat in Diversity

Against the idea of diversity, communism asserts the idea of uniformity: against freedom, inevitability; against choice, compulsion; against democracy, dogma; against independence, ideology; against tolerance, conformity. Its faith is that the iron laws of history will require every nation to traverse the same predestined path to the same predestined conclusion. Given this faith in a monolithic world, the very existence of diversity is a threat to the community future.

— From Remarks by Adlai E. Stevenson to the United Nations in October 1962.
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