

Fundamental Aspects of Dose-Response Relationships and Their Extrapolation for Noncarcinogenic Effects of Metals

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Fundamental differences in dose-response relationships between "stochastic" and "nonstochastic" effects of chemicals are identified and discussed. The difficulties in extrapolating into the low-dose region of dose-response curves are pointed out. In some instances of nonstochastic effects, observations concerning interindividual variability in biological half-time and threshold body burden for symptoms may be used for such extrapolation. An example based on data from the literature concerning effects of methylmercury on the nervous system is given. The confidence intervals of the extrapolated risk-values are computed and discussed in relation to assumptions concerning the mathematical model to be used in the extrapolation process.

Introduction

There are considerable differences in the type of biological disturbance lying behind various effects resulting from exposure to chemical toxicants. It is therefore not surprising that the parameters of fundamental importance for assessing meaningful dose-response relationships also vary for the different types of effects. Stochastic effects, e.g., carcinogenesis, need to be evaluated somewhat differently from many other effects of toxic chemical substances. With carcinogenic effects, the so called no-threshold approach is often advocated for dose-response relationships. In such instances, mathematical extrapolations to low response rates and low doses have been used in connection with safety evaluations. Similar methods for extrapolation may sometimes be used even for nonstochastic effects. This paper will discuss fundamental aspects of dose-response relationships in general and also take up some mathematical and

statistical methods that have been used for the evaluation of nonstochastic effects, methylmercury poisoning being used as an example.

Fundamental Aspects of Dose-Response Relations

Because of its great importance for safety evaluations of toxic substances, the problem of extrapolation of empirical observations to low doses and low response rates has received considerable attention in recent years. Various mathematical models have been proposed for such evaluation of carcinogenesis (1). For stochastic effects, there is no threshold dose for an individual below which he will show no symptoms and above which symptoms are certain to appear. Still, there are interindividual variations in sensitivity, and consequently plots of dose versus probability of effect are conceivably different among individuals. The population dose-response curve is an aggregation of individual plots of dose versus probability of effect. In the case of carcinogenesis, the dose is often expressed as the product of time and intensity of exposure. This is not the case with nonstochastic effects. The relationship between the *in situ* concentration of the proximal carcinogen and the occurrence of cancer

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has not been much studied. Data on such relationships could be expected to be of value in sorting out factors influencing dose-response relationships for cancer, but the scarcity of such data makes any detailed discussion impossible.

The general philosophy of using critical concentrations in critical organs in the evaluation of dose-response relationships for nonstochastic effects of toxic metals has been elaborated upon by the Task Group on Metal Toxicity (2). The terminology used in the following sections of this paper, dealing with nonstochastic effects of metals, will be synonymous with that of the Task Group. The classical definition of the term "dose" will be adopted here, i.e., dose will refer to the amount given or the amount taken in (e.g., gastrointestinally). The critical concentration in the critical organ is defined as that concentration in an individual which gives rise to a certain effect, i.e., the critical effect. This implies that the critical concentration may vary among individuals in a population. Further discussion concerning such interindividual variation in critical organ concentration (critical body burden, or threshold body burden) can be found in the following sections of this paper.

The dose-response relationship is the relation between dose and the proportion of an exposed population that develops a certain effect (e.g., paresthesia). When the dose is defined as the amount taken in, e.g., orally, the dose-response relationship will depend on the interindividual distribution of critical organ concentrations as well as on the interindividual distribution of metabolic parameters (i.e., the absorption, distribution, and retention).

If it is assumed that the metabolic parameters are the same in all individuals, a certain dose always gives rise to the same organ concentration. The cumulative distribution of critical organ concentrations among individuals could then be relabeled into a cumulative distribution of critical doses, i.e. a dose-response curve. Some important issues brought to light by the threshold concept can be isolated under this assumption. Cumulative (population-related) dose-response curves resulting from some cases of distributions of critical organ concentrations (threshold doses) are studied. If the critical concentration (threshold dose) is the same in all individuals, the cumulative distribution takes a single step from 0% to 100% response at this value (Fig. 1a). With a rectangular distribution of critical concentrations (threshold doses) (Fig. 1b) the dose-response curve consists of a straight line between a 0% and a 100% value. As a final example, if the distribution is logarithmic-normal (Fig. 1c), the dose-response curve is identical with a cumulative log-normal distribution. Among these distributions

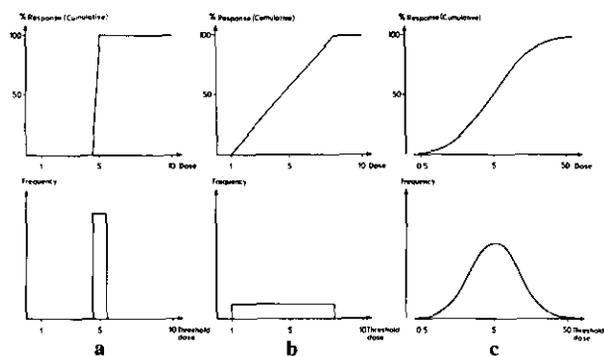


FIGURE 1. Nonstochastic effects: Distribution of critical organ concentrations (threshold dose) are shown in the lower graphs and the corresponding cumulative (population-related) dose-response curves are shown in the corresponding graph above: (a) all individuals in the population have the same critical concentration (dose ≈ 5); (b) rectangular distribution of critical organ concentrations; (c) lognormal distribution of critical organ concentration (threshold doses).

only those shown in Figures 1a and 1b have definite "thresholds" in the dose-response curve, i.e. doses > 0 below which there is no response. General biological experience makes it highly unlikely that distributions with such sharp cut-off values as those in Figures 1a and 1b do exist. However, there may be other types of distributions with zero-response. Curves of the types seen in Figure 1c are frequently found in animal experiments.

In reality, there is not only interindividual variation in critical organ concentration but also in metabolism among various individuals. In principle, no simple relation between the distribution of critical organ concentrations and the dose-response curve then holds. The compounded dose-response relationship depends in a complex way on the relationship between dose and concentration in the critical organ and the relationship between concentration in the critical organ and response, as exemplified by the model for methylmercury poisoning to be given below. It is a compounded or total dose-response curve that can be estimated pointwise in sampled epidemiological investigations and which is of importance in setting safety limits for exposure to the public.

Regardless of whether a dose-response curve is estimated directly from observations or inferred from a combination of data on metabolic variation and concentration/response, it will in practice be difficult to determine its shape in the low-dose region. The response rates extrapolated for low doses are often strongly dependent, even for a given set of observation data, on what assumptions are made as to the underlying mathematical function form (3). This too, will be shown in the example of methylmercury.

In the case of stochastic response or effects, individuals have no definite critical organ concentrations, but individual curves for dose versus probability of effect which may differ among individuals due to varying sensitivity and metabolism. The aggregation up to a population dose-response curve is an averaging procedure, basically the same as in the case in which critical organ concentrations do exist. The resulting curve is now determined by the interindividual variation as well as by the typical shape of the individual curves. Individual relations between dose and probability of effect cannot in principle be observed or estimated but are approximated by dose-response curves found for populations of inbred strains, in which case genetically determined variation is largely reduced. In Figure 2 some individual dose versus probability of effect curves of the "ice-hockey-stick" type are shown together with the resulting population dose-response curve.

Dose-response curves for acutely toxic substances are, as a rule, convex downwards for small dose levels. The curve may be so close to zero for a range of small dose levels that these may be considered virtually safe. The shape of the

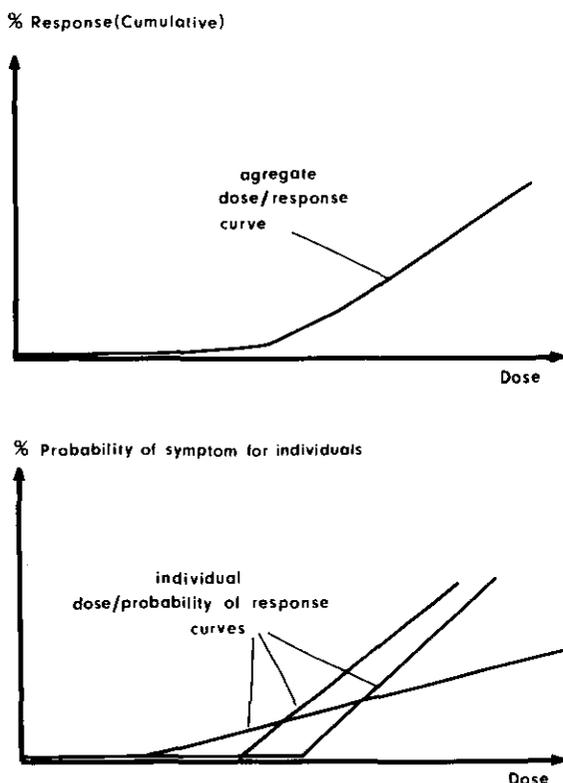


FIGURE 2. Stochastic effects: (bottom) individual dose versus probability-of-effect curves and (top) corresponding (aggregate) dose-response curve for the population.

dose-response curve is difficult to estimate practically for low levels, but if the portion of the curve that can be reliably estimated has a steep slope, and if its continuation downwards intersects the dose axis for some positive dose level, this can be taken as an indication that there exist "virtually safe" levels.

Extrapolation of a Dose-Response Curve for Methylmercury

The assumptions made about the metabolism and toxic effects of methylmercury (MeHg) are as follows. An ingested amount of MeHg is excreted from the body with a biological half-time t . For any profile of daily intakes, the resulting development of body burdens can then in principle be calculated. In particular, after a long time with an average daily dose d (mg) of MeHg, a steady-state body burden of $d(t/\ln 2)$ is gradually reached. The value of t varies among individuals and consequently so does the equilibrium body burden, with mean and standard deviation equal to $d/\ln 2$ times those of the half-time distribution. The critical body burden (leading to, e.g., paresthesia) also varies, independently of the half-time variation. The bivariate distribution of half-time and critical body burden can be plotted (Fig. 3). The probability of poisoning is the probability mass below a line with slope $d/\ln 2$. Computation of that mass for varying d yields the

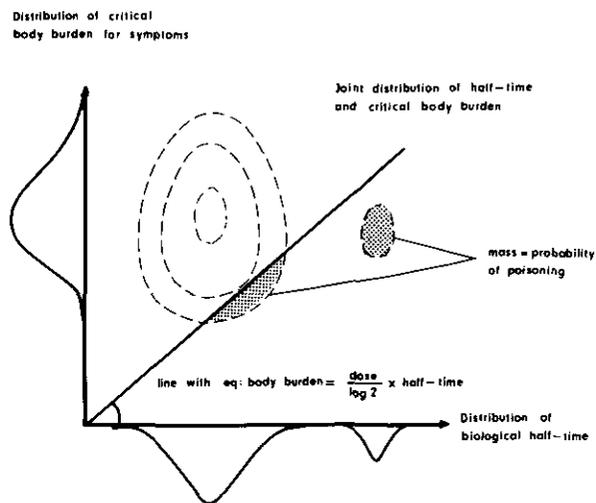


FIGURE 3. Derivation of the joint distribution from interindividual variation in half-times and interindividual distribution of critical body burdens. The line represents steady state body burdens at a certain long term daily intake d combined with the varying half-times along the x-axis. The mass below the line is the probability of poisoning at dose d .

dose-response relationship. A detailed description of the method has been given by Nordberg and Strangert (4).

The distributions of t and of critical body burden were estimated as described below.

Estimation of Interindividual Variation in Threshold Body Burden for Symptoms

In Table 1 are given data according to Bakir et al. (5), consisting of sets of observations concerning the frequency of paresthesia in groups of persons with varying body burdens of methylmercury. The most frequently used distribution types to which these data might fit reasonably well are the log-normal and Weibull distributions. In addition, the background frequency of paresthesia in the population must be estimated. (It is evident that it would be of great value to get more precise data on the background frequency, which may be easily obtained).

Table 1. Observed relationships between body burden of methylmercury (as derived from blood concentrations) and symptoms of paresthesia in persons exposed to methylmercury in Iraq."

Body burden, mg	Number of persons observed	Number of persons with symptoms (paresthesia)
4	21	2
25	19	1
55	19	8
105	17	10
168	25	20
202	17	14
243	4	4

"Data from Bakir et al. (5).

In both bases, a numerical maximum likelihood estimation procedure was used, based upon the fact that in each group of exposed persons, the number of individuals showing symptoms has a binomial distribution. The covariance matrix of the estimates was estimated by the negative inverse of the matrix of second derivatives of the log-likelihood function.

For a log₁₀-normal distribution, the mean value \hat{m} and standard deviation \hat{d} estimated were

$$\hat{m} = 1.949 \pm 0.057$$

$$\hat{d} = 0.345 \pm 0.070$$

with the body burden of 1 mg taken as reference level. This corresponds to a median value of 89 mg for the critical body burden. The background was simultaneously estimated at 6.3%.

For a Weibull distribution,

$$F(x) = 1 - \exp \{ -[(x - w)/b]^k \}$$

w was set equal to zero, and the parameters b and k estimated at

$$b = 124.0 \pm 14.3$$

$$k = 1.40 \pm 0.30$$

This corresponds to a median value of 95.4 mg for the critical body burden. The background was estimated at 7.3%.

Estimation of Interindividual Variation in Metabolism

Interindividual variation in biological half-time has been presented by Al-Shahristani and Shihab (6). They found a normal distribution of the biological half-time of methylmercury with a mean value of 64 days and with a standard deviation of 15 days representing 89% of the population, the rest of the population having 119 days as biological half-time. Although further data on the half-time would be desirable, the uncertainty in the interindividual variation in threshold for symptoms has more influence on the calculated response rates. However, the part of the population with a very long half-time is a high-risk group that has great relative importance at low doses. Their proportion is critical to the calculated values.

Compounded Dose-Response Curves, Taking into Consideration Interindividual Variation in Metabolism and in Thresholds

The dose-response curves resulting from computations taking into consideration both the interindividual variation in threshold body burdens for symptoms and interindividual variation in biological half-time for methylmercury are given in Figure 4. It is evident that the choice of type of distribution has great influence upon point estimates of response for low doses. However, as demonstrated by the confidence intervals at lower doses, such

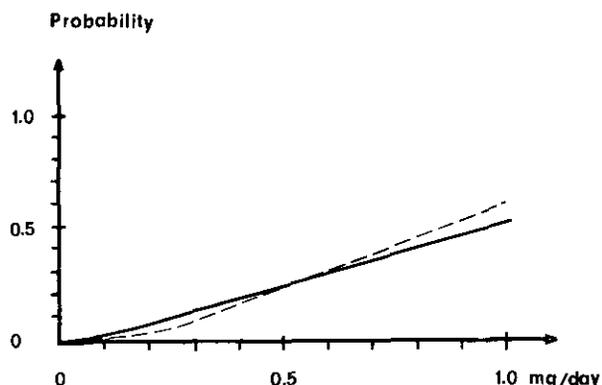


FIGURE 4. Dose-response curves (point estimates of risk) for methylmercury poisoning. (---) log-normal model; (—) Weibull model.

estimates do not exclude relatively high (or low) response rates. For a daily intake of 0.1 mg (in a 50-kg individual) the 90% confidence interval extends with a factor of approximately 3 above and below the point estimate of 2.98% (above background) with the Weibull distribution (Fig. 5a). The point estimate with the log-normal distribution is 0.40%. The difference in point estimates by a factor of more than 7 seems large, but the confidence intervals overlap. There is therefore no clear contradiction between the two mathematical expressions at the dose level 0.1 mg/day. With lower dose levels such as 0.02 mg/day, the extrapolation results from the two mathematical models can no longer be reconciled. The point estimate for the Weibull distribution is 0.32%; with the log-normal 0.00%, the confidence intervals do not overlap (Fig. 5b). Although the (above background) response es-

practical importance at considerably lower response values than those merging into the uncertain background estimate of the present set of data.

Comments and Discussion

Difficulties involved in the extrapolation of responses to low doses have been discussed in many papers. Some general approaches have been proposed for such extrapolation when no mathematical function type can be pointed out as the valid description of the dose-response relation. Mantel and Bryan (7) recommend a log-normal functional form with a conservative standard deviation estimate of one logarithm (to the base 10) per probit, which is on the safe side for most acutely toxic substances (not carcinogens). The value estimated for the present model was 0.345 instead of 1.0.

Another approach is advised by Hoel et al. (1), i.e., linear extrapolation toward zero, assuming no threshold. The risk obtained this way may be compared to the values obtained with the Weibull model. The exponent k was estimated in the present studies to be as low as 1.40, while 1.0 would give an approximately linear portion near zero doses.

Most papers dealing with extrapolation to low doses have studied only compounded dose-response curves. Only in a few instances has it been possible to sort out various factors, e.g., the influence of the variation in metabolism, contributing to the dose-response relationship. It seems that it would be a useful approach to try to gain more knowledge about the fundamental factors that together determine dose-response relationships and to study the influence of each such factor per se. In this way a better understanding of the dose-response relationship will be gained and ultimately lead to a more valid and certain possibility of extrapolating to low response levels. Such studies will also give indications concerning upon what matters to devote further research. In the present case, for example, it is evident that a further definition of the interindividual variation in biological half-time will not add substantially to the final evaluation, whereas data on the proportion with the high half-time as well as more data on the factors influencing the interindividual variation in threshold will be of great value.

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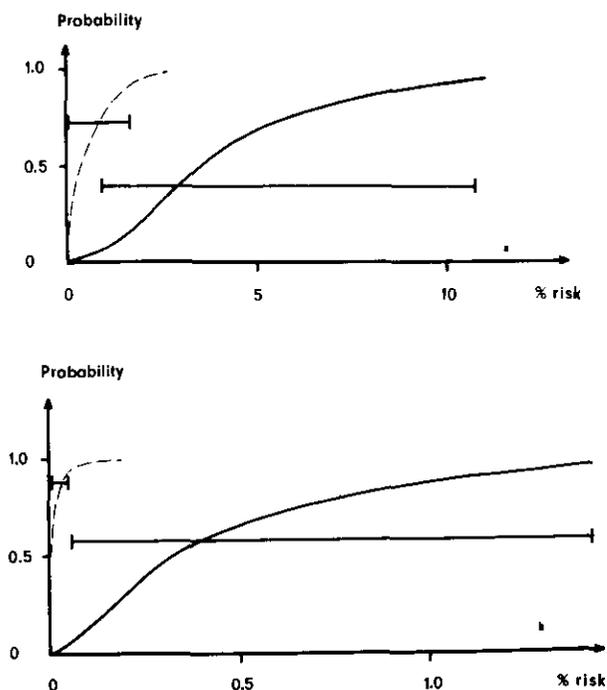


FIGURE 5. Probabilities that given risk values exceed the true value (a) at MeHg dose 0.1 mg/day and (b) at dose 0.02 mg/day: (---) log-normal model; (—) Weibull model. Bars indicate 90% confidence intervals.

timates from the two mathematical models differ from each other, it is evident (with the present set of data) that the uncertainty in the background estimate overrules the practical importance of any such difference. It is usually relatively simple to obtain more reliable measurements of background frequency and the discussion about the difference between the mathematical models therefore may be of

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