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MODEL SELECTION AND PARAMETERIZATION OF THE CONCENTRATION–RESPONSE FUNCTIONS FOR POPULATION-LEVEL EFFECTS

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Abstract—As concentration–response functions for chronic population-level effects of pollutant chemicals, three mathematical models were presented and examined for goodness of fit to published toxicological data that estimated the population-level effects of chemicals in terms of the intrinsic rate of population growth (r). Among the examined concentration–r functions, the power function model, that is, $r(x) = r(0)[1 - (x/\alpha)^{\beta}]$, in which x is the exposure concentration and α and β are parameters, performed with the best fit to each data set. The power function model is characterized by two parameters representing the absolute value of toxicity, α, and the curvature of responses, β. The bootstrap simulation, conducted on the entire data set consisting of all published data that we collected, indicated that the observed variance of β among actual data sets could be mostly explained by the random error variation generated from the bootstrap resamplings. The generic β value, determined from the entire data set and expected to denote the best estimate of β if the variability of β was completely due to random sampling error, was estimated as 1.84. It was implied that the response of the intrinsic rate of natural increase (r) to chemical exposure was nearly quadratic in many cases.

Keywords—Ecological risk assessment Population-level effect Natural increase Dose–response function Ecotoxicology

INTRODUCTION

Proper selection and parameterization of dose–response models are crucial during risk assessment for pollutant chemicals [1,2]. The risk estimation of pollutants at minuscule exposure levels largely depends on the extrapolation models employed.

As for the ecological risk assessment, selection of the relevant mathematical models is difficult, because various endpoints and benchmarks (e.g., no-observed-effect concentration, ecological hazard quotient, reproductive potential, water-quality criteria, and community-level response) are exploited in risk evaluation. Nonetheless, consensus is growing that the population-level effects, rather than the individual-level adverse responses, are more important for estimating the ecological hazards, and that the responses at the two levels can be considerably different in quantity (even though they are closely associated in many cases) [3–5].

The intrinsic rate of natural increase (r) is one of the most comprehensive summary indices that measure the population-level effects, because it represents the potential of a population to proliferate [6]. A population growth rate smaller than the acceptable minimal value that is needed for persistence of populations indicates that the population does not proliferate or replace and, in the future, will go extinct [7–9].

Adverse effects of pollutant chemicals on the intrinsic rate of natural increase can be estimated in several ways. Estimation of age-specific survival and reproduction as a life table under specific exposure concentrations, which is often referred to as life-table evaluation [10], provides estimates of the intrinsic rate of natural increase. A number of studies have estimated the effects of pollutants, using the life-table method, in terms of reductions in the intrinsic rate of natural increase, using mainly phyto- or zooplankton species [11–18]. Other studies have estimated pollutant adverse effects on the intrinsic rate of natural increase with population growth experiments. Experimental populations were censused repeatedly under exposure to chemicals for some period to collect time-series data regarding the population size growing from small initial numbers [19–22]. Hence, data regarding population-level effects expressed in terms of reductions in the intrinsic rate of natural increase are available. Very few studies, however, have examined dose–response models that approximate the adverse responses to exposure by the intrinsic rate of natural increase. The present study reviews published reports estimating responses of r to pollutant chemicals with the life-table evaluation and the population growth experiment. To describe the observed relationships between exposure concentration and responses measured as reductions of r, we propose three mathematical models (i.e., concentration–r models): the power function model, the Weibull model, and the quadratic function model. In addition, we examine the relative goodness of fit among the three models to the observed relationships.

The concentration–r models presented here involve two types of parameters, each representing the absolute magnitude of toxicity, that is, the concentration at which major responses of r occur (i.e., r reduces to 0), and the curvature of responses. These parameters were estimated for each data set, and the statistical properties of the parameters were examined. Generic parameter values were also estimated from standardized entire data sets. The generic parameter values were expected to represent the general trend of responses in r to exposure of chemicals under the assumption that the chemical-specific and the species-specific curvatures of responses were neglected. For the power function model, which showed the best fit to data among the analyzed models, uncertainties in the prediction of

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responses arising from random sampling errors of data in estimating the curvature of responses were evaluated with the bootstrap simulation.

MATERIALS AND METHODS

The endpoint response

In the present analyses, we focus on the intrinsic population growth rate (r) as the endpoint that measures adverse responses of organisms to exposure of pollutant chemicals. In this section, we briefly explain the background on which our analysis is based.

The intrinsic rate of natural increase is the maximum density-independent growth rate of populations [23,24] and, thus, is a general population-level parameter, summarizing various individual-level responses to stress (e.g., inflated mortality, reduced reproduction, and behavioral disorders). The standard definition of r (i.e., the instantaneous density-independent rate of population increase) is embedded in the logistic population growth model:

$$dN/dt = rN(1 - N/K)$$

where N is the population density (i.e., the number of individuals per unit area) and K is the carrying capacity (i.e., the maximum population density). Some mathematical studies have shown that the extinction probability or mean extinction time of populations largely depends on r and K, and that the reductions of the mean extinction time are approximately predicted from reductions in r and K [9,25,26]. The population viability analysis in conservation biology exploits such relationships for predicting the extinction risk of endangered populations from reduced population size or habitat area [27]. The same framework might be successfully applied to ecological risk assessment of environmental pollution by chemicals if the population-level effects of pollutant chemicals were estimated in terms of reductions in r [28]. Thus, estimation of adverse effects of pollutant chemicals to r is one of the most important bases for introducing population viability analysis into the ecological risk assessment of chemicals.

Data source

Published ecotoxicological data and unpublished data from our studies were used as the data source for analyses (Table 1). Two categories of experimental designs are relevant to estimating pollutant effects reducing r: the life-table evaluation tests [12,29], and the population growth experiments [21,22]. The life-table evaluation test examines age-specific survival rate and per-capita reproduction for the full life cycle under specific exposure concentrations. The intrinsic rate of natural increase is estimated from the Euler-Lotka equation

$$\sum_t (l_t m_t e^{-rt}) = 1$$

where l_t and m_t are survivorship and fecundity, respectively, at age t. The population growth experiment is designed to directly estimate changes in population size, for at least several generations, of experimental populations growing from an initially small population size. Most publications that have reported results of life-table evaluation tests have provided estimates of r as determined with the Euler-Lotka equation. We reanalyzed the population growth data to estimate r under different exposure concentrations if r was not calculated in the original publications. The integrated logistic equation,

$$N_t = (N_0K)/[N_0 + (K - N_0)e^{-rt}]$$

where N_0 and N_t are population size at time zero and time t, respectively [23], was used to estimate r with the least χ^2 curve fitting using Mathcad Plus 7 software (Math Soft, Cambridge, MA, USA) and the Levenberg-Marquardt algorithm [30]. Alternatively, the exponential equation was used if the observed population density did not approach asymptotic values due to limited test periods.

*Concentration–*r *models*

We employed three mathematical models as concentration–r functions and compared the goodness of fit to observed data. The properties of r responding to exposure to toxicants, which should be incorporated into proper concentration–r functions, are as follows: to take the maximum value with null exposure, to monotonically decrease with exposure concentrations, and to decrease infinitely below zero rather than asymptotically approaching zero as the exposure concentration increases. The three proposed functions, which satisfy these properties, were the power function, Weibull, and quadratic function models (Table 2). The analyzed models may be merely a subset of all relevant concentration–r models. Nonetheless, the power function and the polynomials are the most general models, which describe continuous responses with arbitrary curvatures. The quadratic model is one of the simplest cases of the polynomials. The Weibull model (i.e., Gompertz function) is one of the most common response functions that are out of these categories [31]. Cumulative normal distribution (i.e. probit function) or other sigmoid functions were excluded from the analyses, because the responses in r do not draw sigmoid curves by the property [3].

The two parameters, α and β, of the power function model are associated, respectively, with the magnitude of toxicity and the curvature of responses in r to exposure concentration (x). The α parameter corresponds to the concentration at which r reduces to zero, and γ denotes the maximum intrinsic rate of natural increase when the exposure is absent ($x = 0$). The Weibull model employed here is modified from the original form,

$$1 - \exp[-(\alpha x)^\beta]$$

so that the above properties are met. The quadratic model is a combination of a linear function and a quadratic function with the weighting terms α and β, respectively.

The best-fit parameter values of the three functions were respectively estimated for each data set with the least χ^2 method using Mathcad Plus 7 software and the Levenberg-Marquardt algorithm [30].

Model selection criterion

To compare relative goodness of fit among the three concentration–r models, we employed the model selection criterion (MSC) as an index measuring the goodness of fit. The MSC is an extension of the Akaike information criterion, which is derived from the maximum likelihood function [31,32]. The MSC is defined as

$$\ln\left[\sum_{i=1}^{n} w_i(x_i - \bar{x})^2 \Big/ \sum_{i=1}^{n} w_i(x_i - \tilde{x}_i)^2\right] - \frac{2p}{n}$$

where x_i is the i-th observed data, $\tilde{x}_i$ is the i-th predicted value, $\bar{x}$ is the mean observed value, n is the number of data, p is the number of parameters, and w_i is the weighting of data [31]. The higher the MSC, the closer the model explains the observed values. Theoretical models that produce MSC values

Table 1. Source of population-level toxicity data relevant to estimate effects on the intrinsic population growth rate

Test species	Chemicals	Reference	n[a]	α (β)[b]
Daphnia pulex, Eurytemora affinis	Dieldrin	[10]	15, 7[c]	0.202 (29.7), 0.0051 (9.17)
Daphnia pulex	Cadmium	[11]	8	0.0131 (0.585)
Eurytemora affinis	Kepone	[12]	7	0.0235 (1.30)
Mysidopsis bahia	Nickel	[13]	5	0.116 (1.19)
Daphnia magna	Disulfiram, zineb	[14]	5, 7	0.0246 (3.37), 0.221 (1.18)
Daphnia magna, Chlorella pyrenoidosa	Cadmium	[15]	4, 6, 6, 5	0.00319 (1.93), 0.0310 (0.295), 0.192 (0.614), 10.5 (0.652)
Daphnia galeata mendotae	Fenvalerate	[16]	5	0.000057 (4.92)
Daphnia obtusa	Chromium	[17]	6	0.105 (23.1)
Daphnia magna	Endosulfan	[18]	7	2.47 (0.516)
Brachionus rubens	Phenol, pentachlorophenol, etc.	[20]	6, 6, 5, 5	44.7 (0.846), 0.227 (6.19), 85.0 (1.19), 14.9 (0.329)
Daphnia magna	Chronic bromide	[21]	7	96.7 (1.22)
Daphnia magna, Salmo gairdneri	Metals	[22]	5, 4	0.00340 (2.98), 0.00118 (1.42)
Mysidopsis bahia	Mercury	[29]	4	0.00158 (2.59)
Echinisca triserialis	Cadmium	[38]	10	0.0159 (1.77)
Daphnia magna	4-Nitrophenol	[39]	6	24.1 (3.07)
Capitella sp.	4-*n*-Nonylphenol	[40]	4	0.319 (2.15)
Lepidodermella squammata	DDT	[41]	4	4.23 (0.478)
Sitophilus orizae	Primiphos-methyl, etc.	[42]	4, 4	0.000470 (2.72), 0.000162 (2.27)
Daphnia pulex	Gamma radiation	[43]	21	70.0[d] (1.99)
Daphnia pulex	Gamma radiation	[44]	5	397.4[d] (8.66)
Daphnia galeata mendotae	Cadmium	[45]	7	0.010 (54.7)
Mysidopsis bahia	Cadmium	[46]	4	0.0291 (1.19)
Ctenodrilus serratus	Cadmium, chromium, etc.	[47]	6, 5, 5, 5, 6, 7, 5, 6, 5, 4, 6, 6	4.81 (1.40), 0.646 (2.37), 0.250 (1.62), 3.25 (1.77), 0.100 (1.33), 5.27 (3.19), 3.49 (0.522), 0.675 (1.48), 0.183 (1.51), 0.451 (0.164), 0.101 (1.14), 0.936 (1.45)
Microcystis aeruginosa, etc.	Endothal	[48]	4, 4, 6, 6, 6, 6	0.114 (1.49), 0.144 (2.53), 0.419 (1.23), 0.546 (0.854), 0.481 (1.20), 0.267 (2.98)
Thalassiosira pseudonana	Amdro (insecticide)	[49]	4	0.00056 (1.06)
Daphnia pulex	Acid stress	[50]	5	2.79 (2.67)
4 *Daphnia* sp.	Copper	[51]	5, 4, 4, 4	0.120 (3.03), 0.068 (5.00), 0.060 (6.25), 0.068 (5.41)
Daphnia magna	Copper	[52]	6, 6	0.101 (5.19), 0.115 (1.20)
Daphnia galeata	LAS12	[e]	12	2.58 (17.2)
Daphnia galeata	*p*-Nonylphenol	[e]	16	0.100 (1.6)

[a] Number of data points.
[b] The least χ^2 estimates of α and β in the power function model (see text).
[c] Multiple numbers indicate more than one data set are included in the referenced source.
[d] Roentgens.
[e] Y. Tanaka and J. Nakanishi, unpublished data.

larger than three are regarded to exhibit an acceptable fit to data, whereas exceptionally good fit (MSC $>$ 6) should be taken as suspects [31]. We calculated MSCs for each data set with the above concentration–*r* models, respectively.

*Standardization of concentration–*r *data to produce an entire data set*

The curvature of response is very sensitive to uncertainties of data, which are caused from unequal test conditions and limited number of data. Relevant estimates of the curvature of responses in *r* for specific chemicals and species are rarely obtained from single experiments with standard sample size. In addition, the large unpredictable fluctuation of the curvature seriously influences risk estimation of chemicals at very low exposure level. Thus, it may be practical to estimate the general curvature of responses in *r* from the entire data set, based on the assumption that specificity of responses or variation of the curvature among different sets of chemicals and species is negligible, and to employ the general curvature in cases when the curvature cannot be precisely estimated due to limitation of data. Essentially the same approach was employed in the

Table 2. Concentration–*r* functions examined in this study

Model	Equations[a]
Power function	$r(x) = \gamma\left[-\left(\frac{x}{\alpha}\right)^{\beta} + 1\right]$
Weibull function	$r(x) = \gamma[-\exp\{(\alpha x)^{\beta}\} + 2]$
Quadratic function	$r(x) = \gamma(1 - \alpha x - \beta x^2)$

[a] x = Exposure concentration, $r(x)$ = intrinsic rate of natural increase.

comprehensive ecological risk estimation based on reproductive potential of aquatic vertebrates [3,5].

Of course, such approaches have many limitations. The data set consists of experiments that are heterogeneous in terms of test conditions (e.g., temperature and water hardness) and exposure schemes (e.g., semistatic or flow-through exposures), even if the test organisms and chemicals are the same. In addition, the referenced experiments were conducted with various test species and chemicals. Properties of responses (e.g., presence or absence of the threshold concentration), which can reflect the curvature of the concentration–*r* curves, may be truly heterogeneous among different sets of chemicals and species.

To produce the entire data set, all data were assembled after being standardized into a dimensionless form. The standardization differed according to the concentration–*r* model that was employed to fit the data. Thus, there were three entire data sets, coming from a common source.

For the general parameter estimation, we employed only those data sets that showed reasonably good fit to each model as the relevant ones. Data sets that produced MSC scores smaller than 1.5 or larger than 8 were excluded from the analysis. These limitations are arbitrary but, nonetheless, noticeably wider than the acceptance criteria. The number of data sets that were excluded was 20 (of 63) for the power and Weibull function models and 23 (of 63) for the quadratic function model. Most data sets that produced MSCs out of these bounds did not exhibit clear systematic responses with exposure concentrations, and they might have caused extra error variation that could confound estimation of curvatures in responses.

For the power function model, we applied the following standardization to all data: The observed intrinsic rate of natural increase was divided by the maximum intrinsic rate, which was observed under the control null exposure concentration, for each data set. The exposure concentration (x) was divided by the α value, which corresponds to the concentration at which r was expected to be zero. Thus, both of the horizontal and the vertical intercepts in the concentration–*r* graph were transformed to unity. The power function model is simplified as

$$R(x^*) = 1 - x^{*\beta}$$

where x^* is the standardized concentration (x/α) and $R(x)$ is the standardized intrinsic growth rate ($r[x]/\gamma$).

Similar standardization of data was employed for the Weibull and quadratic function models. Nonetheless, these models could not be simplified as much as the power function model. For both models, the intrinsic rate was standardized by the maximum intrinsic rate, and the concentration was standardized by the concentration x^* at which the best fit models predicted r to be zero, that is, $r(x^*) = 0$. The two models were converted to $R(x^*) = \exp[-(\alpha x^*)^\beta - 2]$ and $R(x^*) = 1 - \alpha x^* - \beta x^{*2}$, respectively.

Bootstrap simulation

To examine the uncertainties in estimating the curvature of responses in r, we employed the bootstrap method from the entire data set [33]. The bootstrap simulation randomly resampled 5 or 10 data for each trial, then repeated the resamplings for 500 trials for either resampling size. To simulate the experimental design of the toxicological experiment, which is usually designed to estimate responses under systematically dispersed exposure concentrations, the resampling was conducted systematically from five categories of the standardized concentration. The classification of data, based on the standardized concentration, was 0 to 0.2, 0.2 to 0.4, 0.4 to 0.6, 0.6 to 0.8, and 0.8 to 1. One or two data, respectively, for the case of a resampling size of 5 or 10 were randomly chosen from each class of data. The variance of β among the resampled data sets represents the variation purely attributable to random sampling errors.

Uncertainties in r *due to data sampling errors*

Uncertainties in predicting the ecological risk of pollutant chemicals in environments based on the population-level effects may arise due to various reasons, such as dissimilar test conditions [34], acute–chronic or other forms of extrapolation [35,36], and measurement errors of the environmental exposure concentrations. The uncertainties directly resulting from random sampling errors of the toxicological data in the present analysis also include variation among test species and chemicals in adverse responses, interlaboratory variation of test conditions, incomplete repeatability of toxicological data within laboratories due to uncontrollable test conditions, and other factors that influence responses but cannot be specified due to limitation of data.

The power function model was used to evaluate the uncertainty. The uncertainties in the predicted responses of r are decomposed into two components, which are explained by estimation errors of α and β, respectively. The variance component of r due to random estimation errors of α is calculated from the marginal variance of r due to variation of α among resamplings, that is,

$$V_{r(\alpha)} = s^{-1} \sum_i \left\{ r(\alpha_i, \bar{\beta}, x) - s^{-1} \sum_i r(\alpha_i, \bar{\beta}, x) \right\}^2$$

where $r(\alpha_i, \bar{\beta}, x)$ is the marginal value of the intrinsic growth rate estimated from the i-th resampled data set, with β fixed as the generic estimate, and s is the number of resamplings. The same calculation was employed to estimate the variance component due to estimation errors of β, that is, $V_{r(\beta)}$. The variance components, $V_{r(\alpha)}$ and $V_{r(\beta)}$, depend on the exposure concentration, because the sensitivity of r to α and β increases with x.

RESULTS

MSCs for individual data sets

The frequency distribution of MSCs for each concentration–*r* model is illustrated in Figure 1. The mean values of MSCs were 3.08, 2.97, and 2.58 for the power function model, the Weibull model, and the quadratic function model, respectively. The power function model exhibited slightly better fit to data than the other two models. The mean MSC for the power function model is significantly larger than those for the Weibull and the quadratic function model (power function model vs Weibull model, $p < 0.05$; power function model vs quadratic function model, $p < 0.001$). The Weibull model produced slightly better fit than the quadratic function model ($p < 0.05$). Thus, the power function model exhibited the best fit, although the goodness of fit differed only slightly among the models.

Parameter values estimated from individual data sets

The arithmetic means and standard deviations of α and β are listed for the three models in Table 3. Considerable vari-

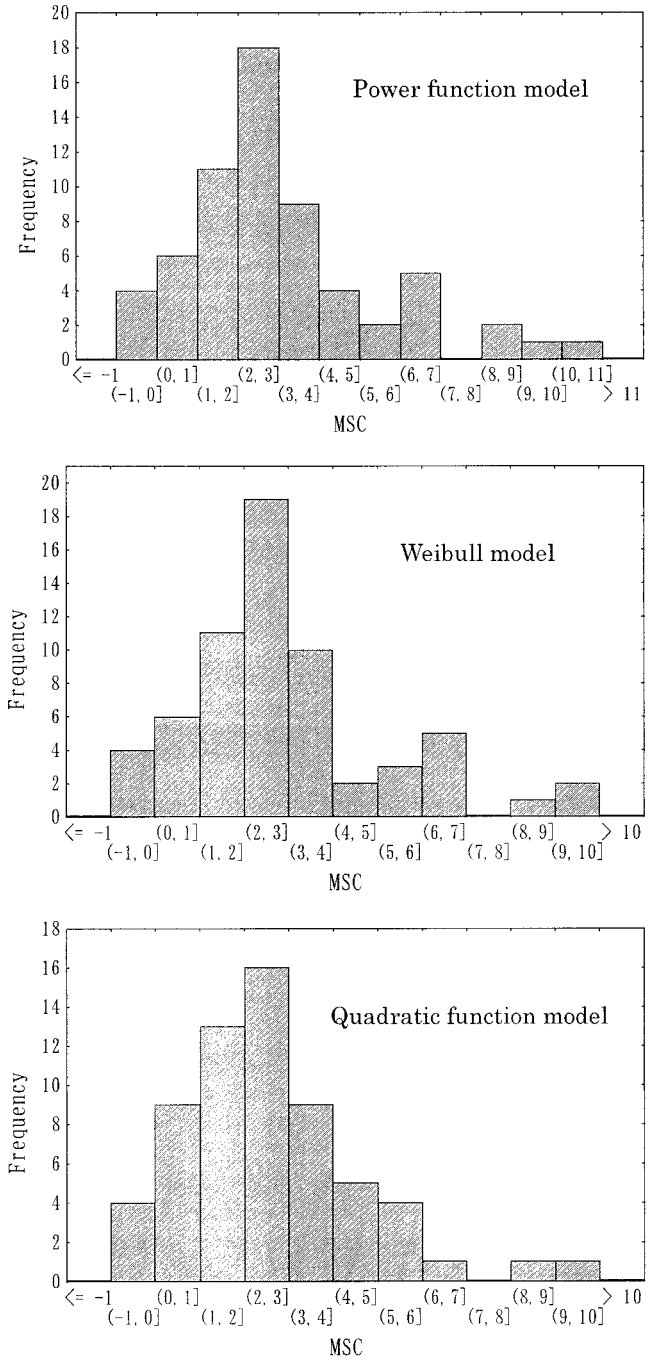

Fig. 1. Distribution of model selection criterion (MSC) values across individual data sets fit to the power function, Weibull function, and quadratic function models, respectively.

Table 3. Arithmetic means ± standard deviations of α and β values in the concentration–*r* models for individual data sets

Concentration-*r* model	α	β
Power function	45.05 ± 78.54	4.48 ± 8.39
Weibull	1.24 ± 2.76	7.87 ± 32.42
Quadratic function	0.47 ± 1.69	9.13 ± 38.8

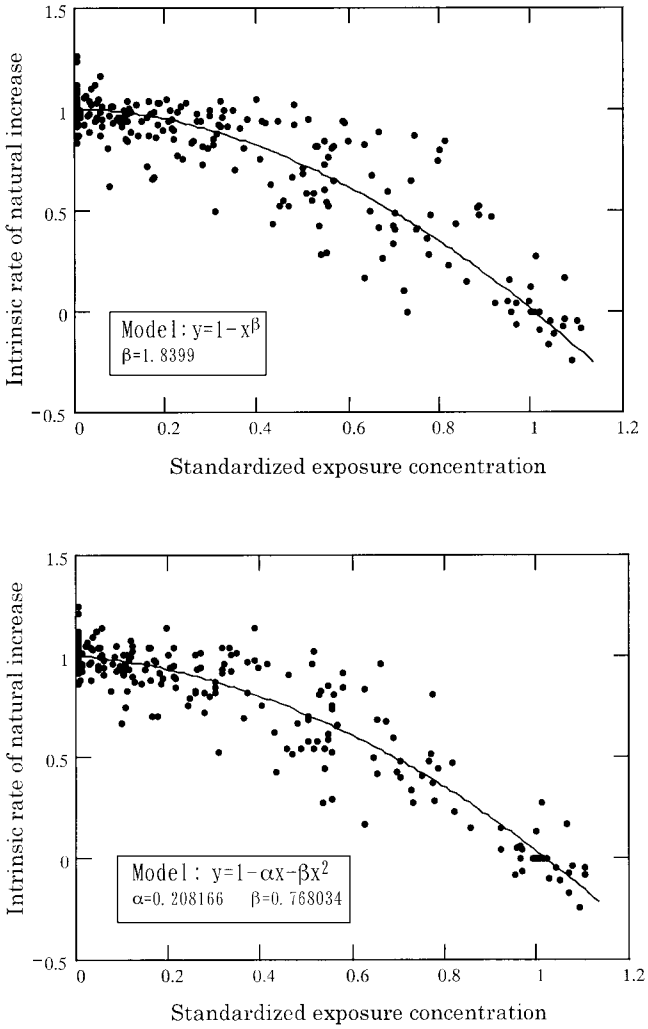

Fig. 2. Scatter plots of the standardized *r* responding to the standardized exposure concentration from the entire data set. Graphs show plots and best-fit curves based on the power function model (upper graph) and quadratic function model (lower graph).

ations were found in β values in all models, which implied the curvature of responses in the intrinsic rate of natural increase varied largely among individual data sets. The variation of α in the power function and Weibull models simply reflected that different pollutant chemicals affected *r* at different exposure concentrations.

The β values in the power function and Weibull models, which strictly represented curvature of responses, were not associated with any chemical or biological variables, such as the octanol-water partition coefficient (K_{ow}), molecular weight of the chemicals, or taxonomic groups of the test species. We found no systematic trends in the curvatures of responses (β) across chemicals and test species.

Estimation of parameters from the all data

The maximum likelihood estimate of β was 1.840 for the power function model from the standardized entire data set (Fig. 2), which was significantly larger than one ($p < 0.001$, paired *t* test for deviations of data from the respective model predictions) but not smaller than two. The responses as a whole are more upward convex than a straight line and might be slightly more linear than quadratic, but they were not statistically significant. For the Weibull model, the parameters were

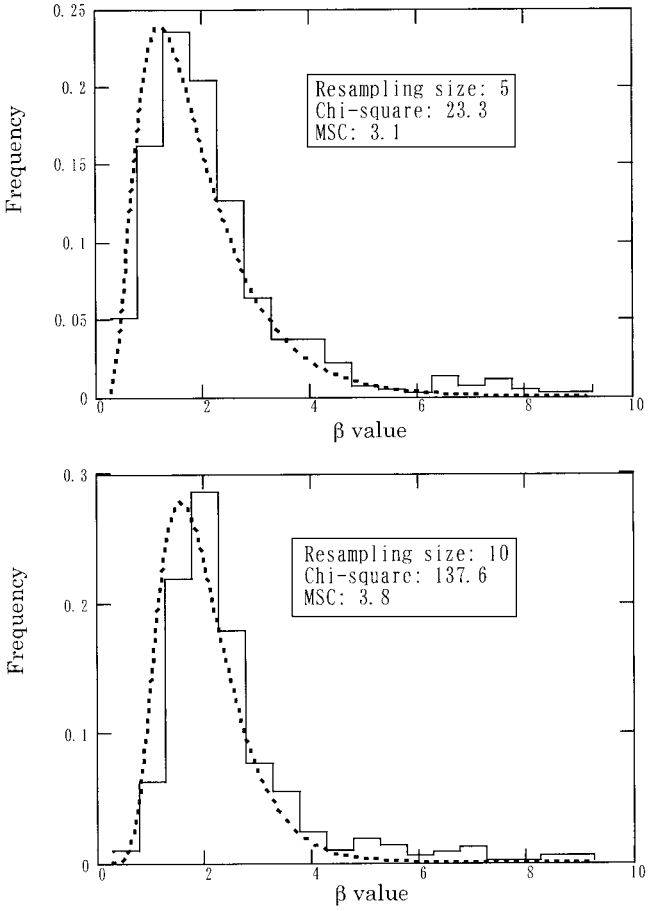

Fig. 3. Frequency distribution of β values in the power function model generated from the bootstrap simulation based on the entire data set with a resampling size of 5 (upper graph) or 10 (lower graph). Broken lines represent the best-fit log-normal curve.

estimated as $\alpha = 0.740$ and $\beta = 1.371$; for the quadratic function model, the parameters were estimated as $\alpha = 0.208$ and $\beta = 0.768$. Because α and β in the quadratic function model are the weightings of the linear and quadratic terms, that α was 0.208 in the quadratic function model implied that the response of *r* was somewhat more linear than quadratic, which was also indicated by the β of 1.840 in the power function model.

The MSCs of the three models to the entire data set were determined as 1.721 for the power function model, 1.779 for the Weibull model, and 2.065 for the quadratic function model. All the analyzed models exhibited poorer fit to the standardized entire data set than to individual data sets (sensu mean MSCs). Relative fit to the entire data set among the three models was reversed from the relative fit to individual data sets (see MSCs for the individual data sets).

Distribution of parameters generated by bootstrap simulation

Because of the good performance with individual data sets and the interpretable parameters, we focused on the power function model. The distributions of β values generated from the resamplings are illustrated in Figure 3. The observed mean (*M*) and variance (*Var*) of β in the natural logarithmic scale among resampled data sets were $M[\ln(\beta)] = 0.709$ and $Var[\ln(\beta)] = 1.229$ with a resampling size of 5 and $M[\ln(\beta)] = 0.694$ and $Var[\ln(\beta)] = 0.324$ with a resampling size of 10.

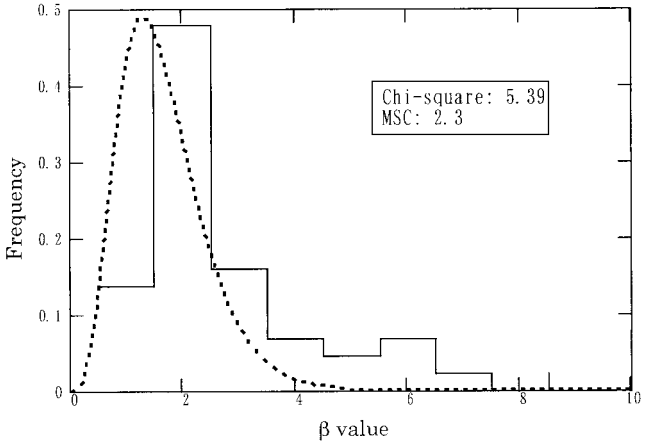

Fig. 4. Frequency distribution of β values in the power function model from the individual data sets. The broken line represents the best-fit γ function.

Both distributions of α and β were approximated by the log-normal distribution. The distributions of the generated data were significantly different from the log-normal distribution in all cases ($\chi^2 = 117.0$ and 23.3 for α and β, respectively, with a resampling size of 5 and 22.0 and 137.6 for α and β, respectively, with a resampling size of 10). Nonetheless, the MSCs indicated that the log normal is one of the marginal or typical well-fit models (MSC = 4.2 and 3.1 for α and β, respectively, with a resampling size of 5 and 5.7 and 3.8 for α and β, respectively, with a resampling size of 10). We regarded the log-normal function as being relevant for an approximate description of data. From the best-fit log-normal distribution, the mean and the variance of the β values in the logarithmic scale were estimated as $M[\ln(\beta)] = 0.185$ and $Var[\ln(\beta)] = 0.305$ with a resampling size of 5 and $M[\ln(\beta)] = 0.450$ and $Var[\ln(\beta)] = 0.149$ with a resampling size of 10. The considerably smaller variances of the best-fit log-normal distributions indicated that the model exhibited more skewed distribution than the resampled parameters.

The mean and the variance of ln(β) in the actual data sets were $M[\ln(\beta)] = 0.795$ and $Var[\ln(\beta)] = 1.086$. Because the sample size of the actual data sets was 5.7 on average (i.e., the geometric mean), a comparison between the variance of β in the actual data sets and in the generated data sets with a resampling size of five may examine the assumption that the observed variability of β among experiments is primarily attributed to random estimation errors. The variance among the actual data sets (1.086) was not statistically different (*F* test) from the variance among the generated data sets (1.229), which supports the assumption. The geometric and the arithmetic means of β among the resampled data sets (resampling size = 5) were calculated as 2.03 and 4.61, respectively, which also is compatible with the observed values among the actual data sets (2.21 and 4.48, respectively).

The distribution of β estimated from the actual data sets was very poorly approximated by the log-normal distribution. The γ distribution was employed as an alternative, but goodness of fit was still unsatisfactory ($\chi^2 = 5.39$ and MSC = 2.3 for β) (Fig. 4).

Based on the sampling variances of α and β that were generated from the bootstrap simulation, the variance of *r* (V_r), which represented uncertainties in the estimates of *r* due to random sampling errors of toxicological data, was estimated according to the causal components ($V_{r(\alpha)}$ and $V_{r(\beta)}$) (Fig. 5).

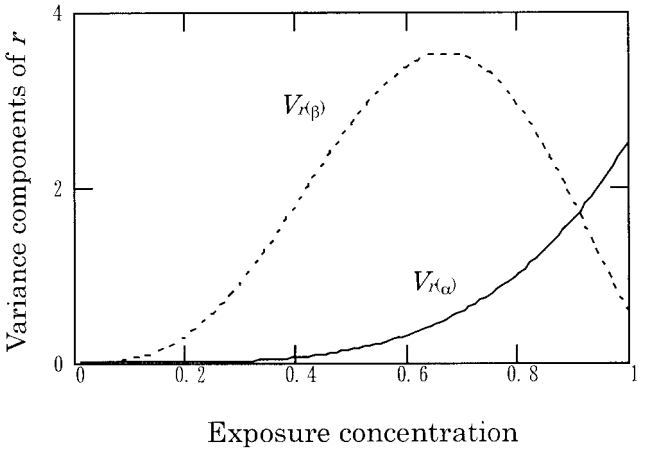

Fig. 5. Variance components of r due to fluctuation of α and β values in random resampling from the entire data set.

The parameter values used to estimate V_r were α = 1.09, β = 2.03, γ = 1.03 (after geometric means), $Var(\alpha)$ = 0.975, and $Var(\beta)$ = 101.1 (from the bootstrap simulation with resampling size = 5). The variance of r due to estimation errors of β is much larger than that due to estimation errors of α with a wide range of exposure concentrations. Uncertainties in predicting r are indicated to be much larger via estimation errors in the curvature of the response function.

DISCUSSION

The present analysis has indicated that the power function model approximated well the responses in the intrinsic rate of natural increase (r) to exposure to chemicals for individual data sets, whereas the quadratic function model approximated well the gross responses in r estimated from the standardized entire data set. There may be other alternative models that predict responses in r better than those analyzed in this study. Nonetheless, the standard sigmoid dose–response functions, such as the logistic (logit) model [31], are not relevant for describing the concentration–r curves without any successful transformation of r, because r is expected to reduce infinitely by responding to exposure to chemicals.

One of the most important properties of these models is flexibility of the curvature of responses, which is denoted by the parameter β (or relative magnitude of α and β in the quadratic function model). This leads to the high goodness of fit of the power function model to responses in r for individual data sets; however, it entails, at the same time, uncertainties in predicting responses of r due to the large sensitivity of β to random sampling errors of data. To circumvent this problem, we used the general β value, which was estimated from the standardized entire data set. This treatment may greatly reduce the uncertainty or bias in estimating β when only a few data of r are relevant to estimate the curvature of responses for specific chemicals and organisms, although it is deficient in that it ignores any chemical-specific or species-specific curvatures between different sets of chemicals and species. In reality, there must be more or less specific curvatures of responses. Nonetheless, provided that the specificity cannot be clearly discriminated from randomness due to limitation of data, it may be more realistic to employ the general value of β and to incorporate the truly specific variation in β into random error variation rather than into estimating specific β values from individual data sets.

We have indirect evidence that random estimation errors in β can predominantly explain the observed variation in β, although we could not conduct any thorough meta-analysis regarding the specificity in β [37]. First, the simulated variance of β, which was generated from the bootstrap resamplings, was not significantly different from the observed variance of β between experiments as estimated from actual data sets. Because variances between the bootstrap resamplings reflect only random sampling errors, the major fraction in the observed variance of β is likely attributable to unpredictable fluctuations of data, and the chemical-specific or species-specific effect is not one of the major causal factors for the variance of β. Second, we failed to find that any factors, such as acute toxicity (e.g., LC50), α values, K_{ow} of chemicals, molecular weight of chemicals, and taxonomic groups of test organisms, were correlated with β. Such findings would have provided indirect support; thus, we do not have any ground to attach greater importance to specific curvatures than random error variation.

Nonetheless, if a chemical-specific or species-specific curvature is estimated with enough precision, we can predict more precise responses with the specific β value than with the generic β value. We need a criterion for choice between the general curvature and the specific curvature to minimize uncertainty and bias.

The simple sensitivity analysis has indicated that the variance components of estimation errors for r, as explained by variation of α and β, respectively, change in relative magnitude with exposure concentrations (Fig. 5). If we are chiefly concerned with minute exposure concentrations, most uncertainties in estimating r must be brought about by estimation errors of β. Thus, utilizing the general curvature may greatly improve the precision of estimated responses of r to exposure at very low concentrations.

The heterogeneous sensitivity of r to α and β across exposure concentrations may highlight a more general problem in parameter estimation for risk predictions. The standard method of parameter estimation does not take into account any a priori distribution of the independent variable (in our case, concentration of chemicals). The least χ^2 fitting, which we employed, does not include any weighting terms for distribution of data. This implies that a parameter estimation that is based on fitting of models to sets of observed independent and dependent variables may not be optimal to predict risk for a presumed distribution of independent variables. In the context of ecotoxicology, the parameters that are estimated with the distribution of exposure concentrations in toxicological experiments (probably uniform in many cases) may not provide the most precise predictions of responses to environmental exposure concentrations, which are considerably lower than experimental exposure schemes, because relative sensitivities of the parameters α and β to r change with exposure concentrations.

The ecological risk estimation based on a concentration–response function is largely influenced by responses at very low concentration and by whether the function has a threshold concentration below which no response is supposed. The models analyzed here do not explicitly assume a threshold. However, the power function and Weibull models are similar to the threshold model in that both predict negligible response at very low concentration. The power function model is most remarkable in this point among the analyzed models. In the power function model, the slope of response with null exposure

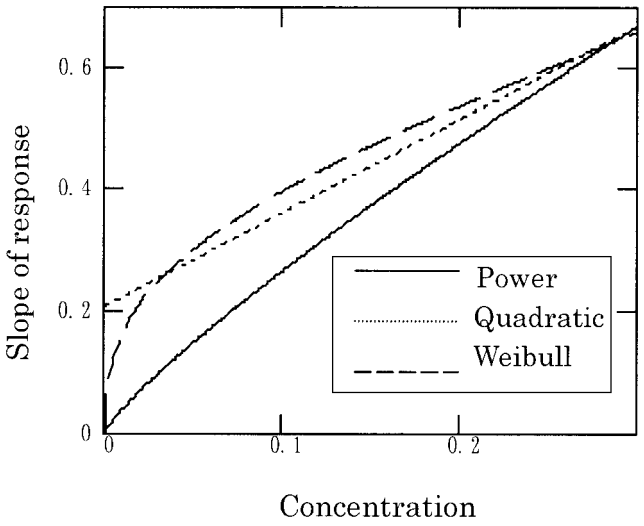

Fig. 6. Slopes of the concentration–*r* functions expected at low exposure concentration. The horizontal axis denotes concentration relative to α (the concentration at which $r = 0$).

(zero concentration), which predicts responses at infinitesimal exposure concentration, is zero regardless of β being larger than one

$$dr(x)/dx|_{x=0} = 0$$

The Weibull model also has zero slope with null exposure, although it inflates at very low exposure concentration (Fig. 6). The quadratic function model has a nonzero slope (2β) with null exposure. We should keep in mind that if we extrapolate the power function model to miniscule concentrations of environmental exposure to estimate ecological hazards of pollutants, we implicitly attach less importance to responses at very low concentrations than we do with other models.

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