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An Approach for Modeling Noncancer Dose Responses with an Emphasis on Uncertainty

Paul S. Price,[1] Russell E. Keenan,[1] Jeffrey C. Swartout,[2] Carol A. Gillis,[1] Heather Carlson-Lynch,[1] and Michael L. Dourson[3]

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This paper presents an approach for characterizing the probability of adverse effects occurring in a population exposed to dose rates in excess of the Reference Dose (RfD). The approach uses a linear threshold (hockey stick) model of response and is based on the current system of uncertainty factors used in setting RfDs. The approach requires generally available toxicological estimates such as No-Observed-Adverse-Effect Levels (NOAELs) or Benchmark Doses and doses at which adverse effects are observed in 50% of the test animals (ED_{50}s). In this approach, Monte Carlo analysis is used to characterize the uncertainty in the dose response slope based on the range and magnitude of the key sources of uncertainty in setting protective doses. The method does not require information on the shape of the dose response curve for specific chemicals, but is amenable to the inclusion of such data. The approach is applied to four compounds to produce estimates of response rates for dose rates greater than the RfD

KEY WORDS: Noncarcinogenic; dose response; probabilistic; uncertainty; reference dose.

1. INTRODUCTION

Currently, noncarcinogenic risks associated with exposure to a chemical are characterized by comparing an estimated dose rate for a compound with an estimate of a dose[4] at which adverse effects are unlikely to occur. For example, the Reference Dose (RfD) Methodology is the standard tool used by the U.S. Environmental Protection Agency (EPA) to estimate a dermal or oral dose that is without appreciable risk of adverse effects.[1,2] A similar approach is also used for inhaled toxicants.[3] RfDs are based on the results of toxicology studies and a system of uncertainty factors.[1,4–6] Inherent in the RfD approach is the assumption that population thresholds exist for chemicals, below which adverse effects are not expected to occur.[7] Hence, in regulatory toxicology doses at or below the RfD are considered to be without a noncancer health risk, while doses above the RfD are assumed to have some (unknown) probability of causing adverse effects. As currently practiced, the approach does not provide a quantitative estimate of the rate of response at any specific dose.

This paper presents an approach for characterizing the probability of adverse noncarcinogenic effects occurring in individuals exposed to specific doses. The approach is based on the system of uncertainty factors currently used in setting RfDs, but extends the methodology to estimate response rates for doses above the RfD. The approach also uses probabilistic techniques to characterize the uncertainty in the response estimates.

The current system of uncertainty factors was first systematically described by Dourson and Stara[4] where the authors defined uncertainty factors in terms of the ratios of doses associated with a chemical's various toxicological endpoints in test animals and humans. Each factor was viewed as a ratio of an "estimated" endpoint

[1] McLaren/Hart-ChemRisk, 1685 Congress Street, Portland, Maine 04102.
[2] U.S. EPA, 26 West Martin Luther King Drive, Cincinnati, Ohio 45268.
[3] Toxicology Excellence for Risk Assessment, 4303 Kirby Avenue, Cincinnati, Ohio 45223.
[4] Hereafter in this manuscript the term dose will be used to mean dose rate.

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Table I. The Current System of Uncertainty Factors[a]

Uncertainty factor	Estimated endpoint	Measured endpoint
Database (UF_D)	The lowest NOAEL observed in a set of chronic and reproductive (or developmental) toxicity studies	NOAEL in any chronic study
LOAEL (UF_L)	NOAEL in a study	LOAEL in a study
Subchronic (UF_S)	NOAEL in a chronic study	NOAEL in a subchronic study
Interspecies (UF_A)	NOAEL in a typical healthy human population	NOAEL in a test species
Intraspecies (UF_H)	NOAEL in a population of sensitive humans	NOAEL in a typical healthy human population

[a] Refs. 1, 3, 6.

to empirically determined or "known" endpoint. Table I presents the current developed uncertainty factors and their associated endpoints. The value of an uncertainty factor used in setting the RfD was loosely defined as an upper bound of the range of ratios that could plausibly occur for any compound.[6]

The uncertainty factors can be divided into two groups: the primary and secondary uncertainty factors (see Table I). The primary uncertainty factors (interspecies [UF_A] and interindividual [UF_H]) deal with the uncertainty in using a NOAEL from a chronic animal study to estimate a dose that is without appreciable risk to a sensitive human population. The secondary factors differ from the primary factors in that they are used to define a high quality chronic animal NOAEL based on lesser quality toxicology data (a subchronic NOAEL, a chronic LOAEL, or a NOAEL from a single study).

As discussed by Barnes and Dourson,[1] the value of the RfD is established by the equation:

$$\mathrm{RfD} = \frac{\mathrm{NOAEL}}{\prod \mathrm{UF}_i} \qquad (1)$$

where $\prod \mathrm{UF}_i$ is the product of the i uncertainty factors required for each chemical.

Traditionally, a single number is used for each of the uncertainty factors. EPA and other regulatory agencies have viewed these values used as loose upper bounds to the range of values that occur across various chemicals.[6] Therefore the RfDs established using the traditional uncertainty factor values should be viewed as the loose lower bound of the uncertainty in an estimate of a dose that is without appreciable risk of deleterious noncancer effects in even sensitive individuals.[2]

The probability that a dose that is without appreciable risk to sensitive individuals will be above a specific dose can be evaluated using a Monte Carlo model of Eq. (1).[8] Under this approach, the distributions of the possible values for a compound's uncertainty factors are described by probability density functions.

2. DESCRIPTION OF THE APPROACH

2.1. Basic Description

Table II presents the nomenclature used in describing the proposed approach. The proposed approach is based on three assumptions. First, the threshold of a compound's adverse effects in human populations (ED_{0h}) can be characterized using the current system for establishing RfDs. Second, the ED_{50h} can be characterized based upon an ED_{50} observed in test animals (ED_{50a}) and the interspecies uncertainty factor, UF_A. Third, the responses at doses between the two doses, ED_{50h} and ED_{0h}, can be conservatively characterized based on a simple dose response model.

The approach uses a probabilistic model of dose response that is based on the uncertainty in the ED_{0h} and ED_{50h}. The uncertainty in the values of ED_{0h} and ED_{50h} are in turn characterized by the uncertainty in the values of UF_H and UF_A[5] for the compound and toxicological data such as the $NOAEL_a$ (or $NOAEL_{he}$) and the ED_{50a} or (ED_{50he}). The output of the model is an estimate of the uncertainty in the response (R_n) that occurs at a dose rate.

2.1.1. Derivation of ED_{0h}

The ED_{0h} is estimated using a Monte Carlo model of the equation used for setting RfDs. As discussed

[5] While this paper only addresses compounds with RfDs established using the two primary uncertainty factors UF_H and UF_A, the approach is also capable of incorporating the secondary uncertainty factors, UF_D, UF_L, and UF_S. Incorporation of these factors will be the subject of future publications.

Table II. Dose Response Nomenclature Used in This Paper

ED_{50a}	—	A dose causing any adverse effect in 50% of animals. The ED_{50a} will be taken from the "critical study."[a]
$NOAEL_a$	—	The largest reported dose that does not cause a statistically significant occurrence of adverse effects in a group of test animals as determined by the critical study for the compound.
ED_{Ra}	—	The dose that causes a response in R% of the animals.
ED_{50h}	—	The dose estimated to cause one or more adverse effects in 50% of the humans. The effects do not necessarily include the critical effect that provided the basis for the NOAEL in the animal study.
ED_{0h}	—	The largest dose at which no adverse effects occur in humans, including sensitive individuals.
$NOAEL_{he}$	—	The largest reported dose that does not cause a statistically significant occurrence of adverse effects in a group of typical healthy humans.
ED_{Rh}	—	A dose that causes a response in R% of the humans receiving the dose.

[a] The critical study is the study that establishes the "critical" effect for a compound. The highest NOAEL in that study provides the basis for the RfD.

above a Monte Carlo model of this equation can be viewed as a model of the uncertainty in the estimate of a dose that is without an appreciable risk to a sensitive individual. The formula for deriving the ED_{0h} from a $NOAEL_a$ established in a chronic animal study is given in Eq. (2):

$$ED_{0h} = NOAEL_a/UF_H UF_A \quad (2)$$

The formula for deriving the ED_{0h} from a $NOAEL_{he}$ established in a human epidemiology study of typical healthy individuals is given in Eq. (3):

$$ED_{0h} = NOAEL_{he}/UF_H \quad (3)$$

The result of this approach is a distribution of values for ED_{0h} that reflects the uncertainty in the estimate associated with extrapolation from test data.

This approach assumes that the RfD is a lower bound to an estimate of a zero effect level (a population threshold). This assumption could be questioned since the RfD is only asserted to be "without appreciable risk." In addition, discussions of RfD for certain substances have made it clear that the standard does not protect the "hypersusceptable" individual.[6] Therefore it is necessary to consider the implications of small but finite risks that could occur for certain chemicals at the doses predicted by Eqs. (2) and (3). In the following discussion we assume that Eqs. (2) and (3) will predict the uncertainty in the ED_{0h}. The impact of allowing a small but finite risk in the prediction is discussed in Sec. 2.3.

2.1.2. Derivation of ED_{50h}

The ED_{50h} is estimated based upon the toxicology study that provides the basis for the RfD (the "critical" study). If the study is a laboratory animal study, the formula to derive the value of ED_{50h} is given in Eq. (4):

$$ED_{50h} = ED_{50a}/UF_A \quad (4)$$

The uncertainty in the estimate of an ED_{50h} from the results of a laboratory animal study includes the uncertainty in the estimate of ED_{50a} and the uncertainty in the interspecies extrapolation. The result of Eq. (4) when UF_A is expressed as a distribution is a distribution of dose rates that reflects the uncertainty in ED_{50h} for the compound.

The value of ED_{50h} for a compound where the RfD is based on human epidemiology data is taken directly from observed data. Uncertainty in the ED_{50h} based on human studies is, therefore, limited to the experimental uncertainty in the value.

In practice and in concept, UF_A has been applied to a NOAEL rather than an ED_{50}.[1,4] Therefore, it is reasonable to consider whether the same probability density function of UF_A used in extrapolating from a NOAEL in animals to a threshold in "average healthy" humans (ED_{0he}) can be used to extrapolate from ED_{50a} to ED_{50h}.

As discussed above, humans are believed to be more heterogeneous than test animals. As a result it is believed that there is greater diversity in individual responses in human populations than in small groups of a single-strain of animals tested under controlled and relatively uniform conditions. Thus, dose response slopes for animals are expected to be steeper than those for humans. Because of this difference in the slopes of the dose response curves, the ratios of the ED_{50a} to ED_{50h} for a group of chemicals are expected to be smaller than the ratios of ED_{0a} and ED_{0he} (as estimated by UF_A) for the same groups of chemicals. Therefore, using UF_A as a means of estimating ED_{50h} from ED_{50a} will systemati-

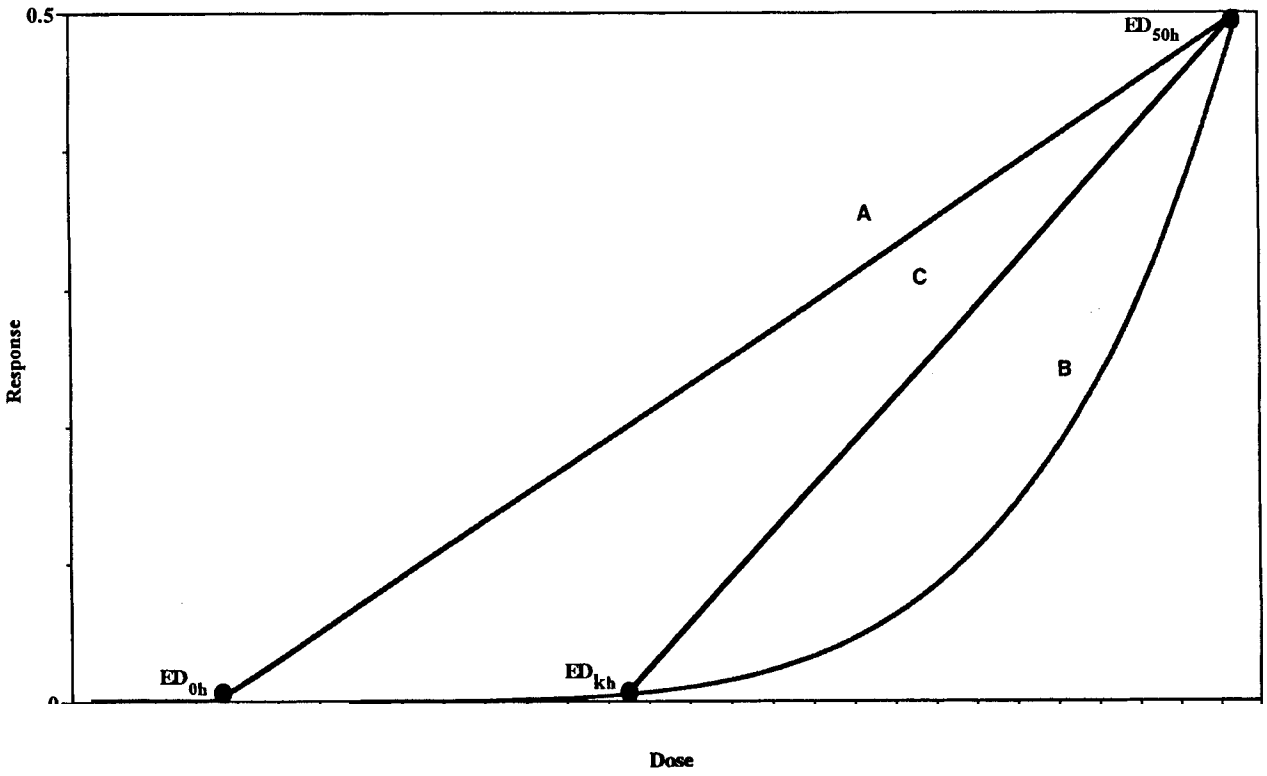

Fig. 1. Dose response curves for a hypothetical noncarcinogen in humans. Line A is a linear model. Line B represents the actual dose response curve of the compound. Line C is a linear model of the response above a small but finite response of K.

cally underestimate the ED_{50h} value (i.e., predict values of ED_{50h} that are lower than the actual values).

2.1.3. Modeling Dose Response at Doses Between ED_{50h} and ED_{0h}

To illustrate our approach, we use a simple linear dose response relationship that is intended to be a conservative characterization of the actual dose response curves for individual chemicals in humans (Fig. 1). Dose response modeling has not been routinely used to evaluate the risks of noncarcinogenic effects because of the difficulties in measuring dose response relationships in animal studies and problems in determining the implication of the dose response findings in animals for dose response relationships in humans populations that include sensitive individuals. The approach presented in this paper avoids this difficulty by assuming that whatever the true dose response curve is in the human population, (including sensitive subpopulations), it will fall below a slope of a line passing through the ED_{0h} and ED_{50h}, (line A in Fig. 1). That is, between the threshold and the dose causing a 50% response, the true dose response curve is assumed to be sublinear (line B in Fig. 1). This assumption will hold true for all compounds that have upward curving dose response curves in both the general and sensitive populations, and where the size of the sensitive subpopulations are small relative to the general population.

2.2. Dose Response Modeling

The dose response model is derived in the following manner. By definition, the ED_{50h} and ED_{0h} are two points on the dose response slope. They define both the slope of the nonzero portion of the dose response relationship and the point at which the response rate becomes zero (the ED_{0h}). The response at a dose above the ED_{0h} is given by:

$$R_h(d) = (d - ED_{0h})\,(M) \qquad (13)$$

Where $R_h(d)$ is the probability that an individual receiving a dose, d, will display the noncarcinogenic effect; and M is the slope of the dose response between ED_{50h}

and ED_{0h}. The value of M is given by the ratio of the change in the response and the change in the dose for the two points on the response line, ED_{50h} and ED_{0h}. The change in the response is simply 0.5–0 or 0.5. The change in the dose is ED_{50h}–ED_{0h}. Therefore:

$$M = 0.5/(ED_{50h} - ED_{0h}) \quad (14)$$

The dose response equation for a compound with a chronic animal NOAEL can be derived by the following approach. Substituting the definitions of M (Eq. 14), ED_{50h} (Eq. 4), and ED_{0h} (Eq. 2) into Eq. (13), we get:

$$R_h(d) = (d\text{-NOAEL}_a/(UF_H UF_A)) \\ (0.5/((ED_{50a}/UF_A) \\ - (NOAEL_a/(UF_H UF_A)))) \quad (15)$$

which reduces to:

$$R_h(d) = 0.5\,(dUF_H UF_A - NOAEL_a)/ \\ (ED_{50a} UF_H - NOAEL_a) \quad (16)$$

By a similar argument, the dose response equation for a compound with a NOAEL established in an epidemiology study of average health humans can be shown to be given by:

$$R_h(d) = 0.5(dUF_H \\ - (ED_{0he}))/(ED_{50h} UF_H - NOAEL_{he}) \quad (17)$$

Since a response cannot be greater than 1.0 or less than 0, both dose response relationships must be truncated such that:

$R_h(d)$
$= 0$ if $d < NOAEL_a/UF_H UF_A$
$= 1$ if $d > 2ED_{50a} - (NOAEL_a/UF_H UF_A)$

for a compound with a chronic animal NOAEL and:

$R_h(d)$
$= 0$ if $d < NOAEL_{he}/UF_H$
$= 1$ if $d > 2ED_{50h} - (NOAEL_{He}/UF_H)$

for a compound with a NOAEL established in a human epidemiology study.

As discussed above, our approach assumes that the true dose response curve for compounds will be sublinear. Algebraically, it can be shown that dose response curves which are symmetrical, monotonically increasing, and sublinear below the ED_{50} will be supralinear above the ED_{50}. That is, the actual response above the ED_{50} will be underestimated by the extension of a linear dose response that passes through the ED_0 and ED_{50}. Therefore, the estimates of $R_h(d)$ that exceed 0.5 should not be regarded as conservative.

2.3. Impact of Residual Risk at the RfD

As discussed above the Eqs. (2) and (3) predict the uncertainty in an estimate of a dose that is without appreciable risk. For certain substances this may correspond a small but finite rate of response, k. For these compounds, the approach would estimate the risks that would occur between a response of k and 50% response, see line C in Fig. 1. In this circumstance Eqs. (16) and (17) produce estimates of a dose that causes an incremental response R_h above k. The total risk associated with this dose is thus $R_h + k$. Where k is small in comparison the response, R_h, it may be ignored. However, if the equation is used to estimate risk specific doses for very small values of R_h, such as 10^{-6}, then the magnitude of k should be taken into consideration.

3. APPLICATIONS OF THE APPROACH

This section presents two applications of the approach. In the first application two hypothetical compounds are used to provide a general description of the approach and the implications of the results for RfDs that are established with different uncertainty factors. In the second application the approach is applied to four compounds. In both applications the level of the residual risk, k, is assumed to be zero.

3.1. Application to Two Hypothetical Compounds

The first of the two hypothetical compounds is defined as having an RfD that is based on a chronic laboratory animal NOAEL; the second compound as having an RfD based on a NOAEL from a long-term epidemiology study of typical healthy humans. The NOAELs for the studies were selected so that the application of the traditional uncertainty factors would result in the same RfD (0.01 mg/kg-day) for both compounds. Dose response curves are generated for both compounds and the uncertainty in the dose response curves is characterized.

3.1.1. Case 1: Chronic Animal NOAEL

The first compound has a NOAEL of 1 mg/kg-day and an ED_{50a} of 10 mg/kg-day from a high quality chronic bioassay. Additional chronic and short-term studies are available and constitute a "complete" database for the compound. Under traditional regulatory

guidance, two primary uncertainty factors UF_H and UF_A would be used in setting the RfD.[6] Using values of 10 for these two factors, the RfD for the compound is:

$$RfD = NOAEL/UF_AUF_H = 1/(10)(10) = 0.01 \text{ mg/kg-day}$$

In this analysis, we assume that the probability density function of UF_H and UF_A is given by a displaced lognormal distribution.[9] The distribution is defined by:

$$\tau + 10^{(\text{Normal}(\mu,\sigma))}$$

where μ is 0.3349, σ is 0.3765, and τ is 1.0. The distribution has a minimum value of 1, a median value of 3.2, and a 95th percentile of 10.

This distribution was developed to be consistent with general definition and concept of uncertainty factors.[2,4,6,10,11] First, the uncertainty factor of 10 has been regarded as a loose upper bound to the true value. The distribution will select values less than 10, 95% of the time. Second, by definition, UF_H cannot be less than 1 for any chemical and, in general, the UF_A is expected be greater than 1 for most chemicals due to the effect of allometric scaling. The distribution will always select values of UF_H and UF_A that are greater than 1. Third, it is assumed that values at the extremes are less likely than values nearer the median. This assumption is based on the interpretation of uncertainty factors as representations of the variability of natural processes. The distribution has a greater probability of being close to the median than at the extremes.

Fourth, it is generally assumed that the underlying natural processes contributing to this variability are multiplicative rather than additive. This assumption implies that the distribution of the logarithms of the values should be more normal than the actual values. As a result, the uncertainty factors are considered to be normally distributed in log space. This assumption is consistent with the traditional practice of using the log-transformed dose in dose response modeling and in the common usage of uncertainty factors (such as 10 or $10^{0.5}$) in the RfD methodology.[10] Finally, empirically derived distributions for many of the uncertainty factors are lognormally distributed.[8,12–16]

The dose response model begins by selecting values of UF_H and UF_A. The values of UF_A and UF_H are randomly selected from the distributions discussed above. Once the values are selected, the equation for R_h is created (Eq. 16) and the responses at selected doses are calculated. The doses used in the model encompass a range from the traditional RfD to a dose 500-fold higher. Once the model selects values for d, UF_A, and UF_H, Eq. (16) is used to determine the response that is the probability of adverse effects occurring in the individual receiving the dose (R_h). The model then saves the values of d and R_h as a set of matched values. The model repeats the process 5000 times for each of the dose rates.

3.1.2. Case 2: Chronic Human NOAEL

The second compound is assumed to have a NOAEL of 0.1 mg/kg-d and an ED_{50he} of 0.3 mg/kg-d in an epidemiology study of typical healthy individuals. Additional chronic and short-term studies are available and constitute a "complete" database for the compound. Under traditional regulatory toxicology only UF_H would be used in setting the RfD. Using a value of 10 for the factor, the RfD for the compound is:

$$RfD = NOAEL/UF_H = 0.1/(10) = 0.01 \text{ mg/kg-day}$$

The same distribution for UF_H is used in both Case 2 and Case 1. The response rate for each dose rate was calculated based on Eq. (17). The model was run 5000 times using the same dose rates as Case 1.

3.2. Results of the Hypothetical Case Studies

Figure 2 presents the a plot of the 5th, median, and 95th percentiles of the distribution of response rates for the doses for Case 1. At doses 10 times higher than the RfD, the median estimate of the response is 0.001 with a 95% certainty that the response will be less than 0.04. At a dose 50 times higher than the RfD, the median estimate of response is 0.07 with a 95% certainty that the response will be between 0.3 and 0.02. Table III presents the results of these two studies in tabular form.

Figure 3 presents a comparison of the median and 95th percentiles for Case 1 and 2. While both compounds have the same RfD, their dose responses are very different. The second compound has a much steeper dose response slope than the first. At a dose of 10 times the RfD, the 95% certainty limit was 0.16 or 4 times higher than the equivalent value for the first compound.

One interesting result of the dose response model for the second compound is the lack of uncertainty as the response rate approaches 0.5. This lack of uncertainty results from the assumption of that there is no uncertainty in the experimentally defined ED_{50h}. In contrast, the ED_{50h} for the first compound has considerable uncertainty since it is estimated based on the ED_{50a} and

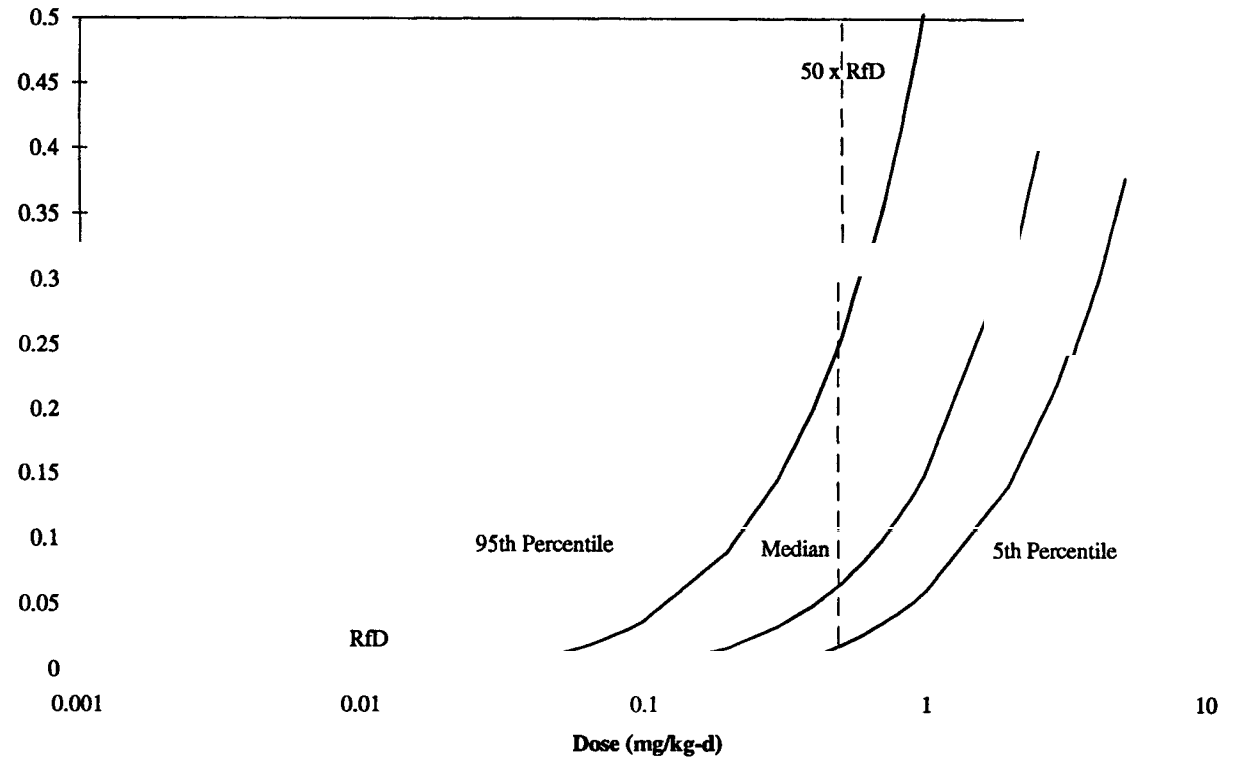

Fig. 2. Dose response curves for Case 1.

Table III. Results of the Two Hypothetical Case Studies

Dose	Multiple of RfD	5th Percentile response	Median response	95th Percentile response
Case study 1				
0.01	1	0	0	0
0.05	5	0	0	1.3E-02
0.1	10	0	1.4E-03	3.7E-02
0.2	20	0	1.7E-02	9.1E-02
0.5	50	1.9E-02	6.6E-02	2.5E-01
1	100	6.0E-02	1.5E-01	5.2E-01
5	500	3.8E-01	8.1E-01	1
Case study 2				
0.01	1	0	0	0
0.05	5	0	3.4E-02	6.8E-02
0.1	10	7.1E-02	1.3E-01	1.5E-01
0.2	20	2.9E-01	3.1E-01	3.3E-01
0.5	50	8.5E-01	8.7E-01	9.3E-01
1	100	1	1	1
5	500	1	1	1

UF_A. Therefore, the different percentiles of uncertainty in the dose response for the first compound do not converge, as they do for the second compound.

3.3. Application of the Approach to Four Compounds

The approach was applied to four compounds of concern to environmental risk assessors, Alachlor, Paraquat, Pentachlorophenol, and Hexachlorobenzene. All four of these compounds currently have RfDs on the IRIS database.[17] Table IV presents toxicological information for the compounds. The RfDs for all four compounds are established using a cumulative uncertainty factor of 100 based on values of 10 for UF_A and UF_H. In addition, the critical effects for all four compounds are dichotomous effects.

Because effects are dichotomous the data can be fitted to dose response models and the ED_{50a} can be readily estimated. The critical studies for all four compounds contain multiple dose groups, including dose groups where the response was greater than 50%. Table III also presents estimates of the ED_{50} for each of the compounds. The value of the ED_{50} was taken from the maximum likelihood estimate of the ED_{50} calculated using the program BENCHMARK.[18] The program was run using a Weibull model with a threshold assumption.

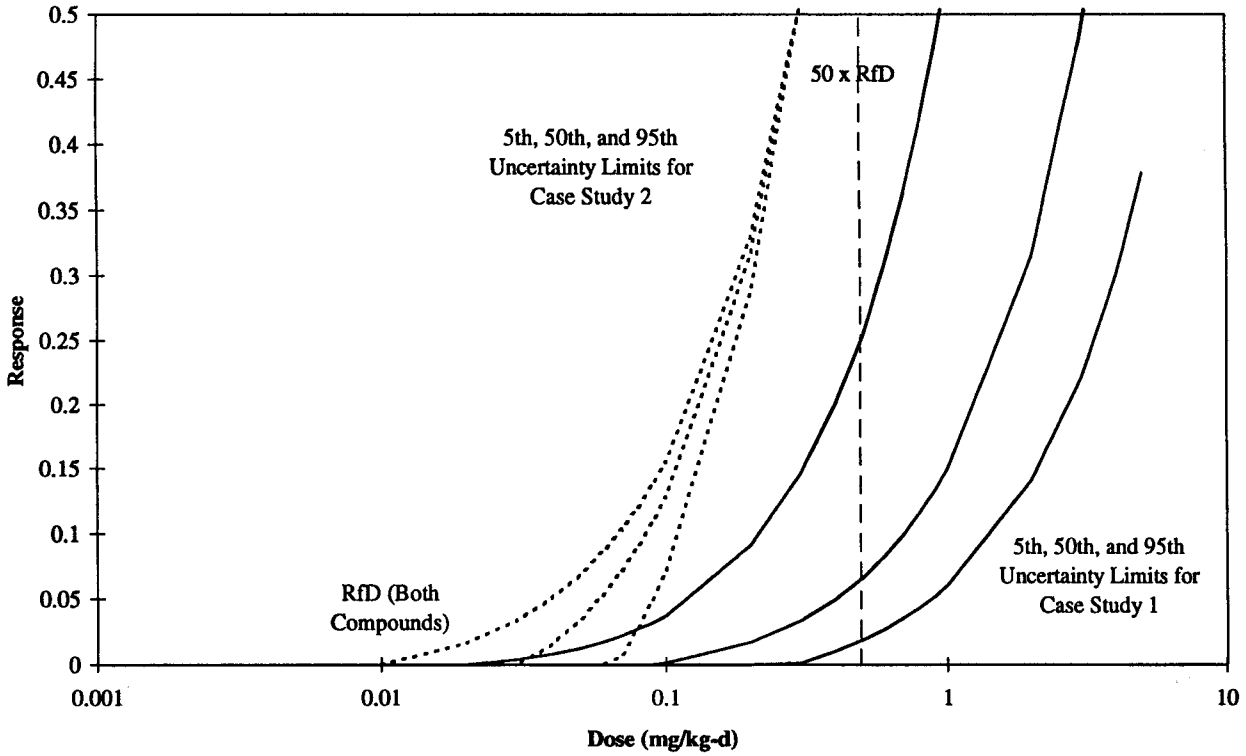

Fig. 3. Dose response curves for Cases 1 and 2.

Table IV. Toxicological Information for the Four Compounds[a]

Compound	Endpoints	NOAEL (mg/ kg-day)	ED_{50} (mg/ kg-day)
Alachlor	Liver	1	9.9
Paraquat	Chronic pneumonitis	0.45	1.1
Pentachlorophenol	Liver and kidney effects	3	22
Hexachlorobenzene	Liver effects	0.08	0.80

[a] Refs. 17, 27.

Figure 4 presents the estimates of the median and 95% certainty limits for the response rates of the four compounds. All four compounds have the same estimates of the number of multiples of the RfD that are associated with the best estimate and upper confidence limits of the ED_{0h}. However, the compounds differed in their slopes. As a result, the median estimates of response at a dose rate 10 times higher than each of the compounds' RfDs resulted in response rates ranging from 0.01 to 0.04.

4. DISCUSSION

This approach is designed to be conservative with respect to the estimate of the ED_{50h}, extrapolation uncertainty, and compounds with sublinear dose response curves. The model is, however, adaptable to any dose response assumption. If there is evidence that a compound follows a supralinear dose response, then the model can be fitted to the supralinear response curve.

The distributions of the uncertainty factors used in the above applications are derived from existing guidance on setting RfDs. Therefore, it is not surprising that the results of the model are consistent with current regulatory views concerning dose response rates for noncarcinogens. Specifically, the model indicates that compounds with RfDs established with values of 10 for UF_A and UF_H will have the following properties:

- dose rates at or below the RfD have a high probability (>95%) but not a certainty of causing zero risk to sensitive individuals;
- for many compounds the incremental responses associated with dose rates that exceed the RfD by factors of 2–5 are small ($R_h < 10^{-4}$) and there is a 95% chance that they are zero; and
- the probability of high rates of adverse effects ($R_h > 0.1$) greatly increases for dose rates that exceed the RfD by factors of 20–100.

The large amounts of uncertainty in the values of UF_A and UF_H are indicated by the large differences between

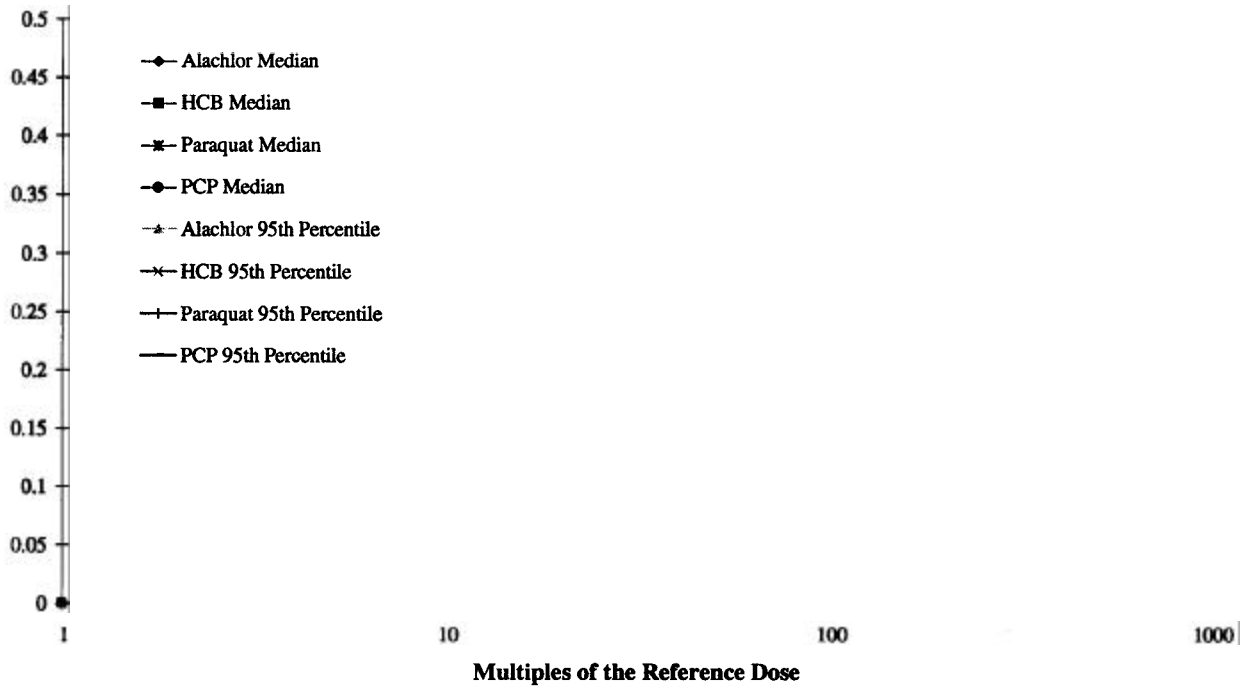

Fig. 4. Median and upper limits of the 90% confidence interval for the dose response curves.

the 95th percentile and the median estimates of the dose response curve. The model also provides insight into the differences in the risks associated with exceeding RfDs established with different uncertainty factors. In general, the smaller the total uncertainty factor used in setting a compound's RfD and the smaller the ratio between ED_{50a} and ED_{0a}, the more rapidly risks will increase as doses exceed the RfD.

The definition of the endpoint being modeled by the approach is also somewhat ambiguous. The critical effect (the first one observed with increasing dose) is the basis for the parameterization of the model. However, there is a great deal of uncertainty as to whether this effect will be the actual effect observed in humans. In general, correspondence and sequence of effects between humans and test species should not be assumed. In addition, any dose response model based on a single effect will underestimate the overall impact of the toxicant. Other effects, or more severe manifestations of the modeled effect that would appear at higher doses are not accounted for. A more appropriate approach would be to use all adverse effects, in combination, as a surrogate for nonspecific manifold effects in humans. Therefore, we recommend that the ED_{50a} be determined on the basis of all adverse effects. That is, the ED_{50a} should be defined as the dose that produces any type of an adverse effect in 50% of the test animals. This approach requires that individual animal data be available and that there is some assurance that the critical toxicological endpoints were evaluated.

Because of these limitations, the model should not be used to predict response rates for specific effects such as reproductive effects, liver toxicity, or central nervous system depression in humans. The model can, however, be used to provide an estimate of the overall impact (occurrence rate of one or more adverse effects) in humans from doses above the RfD and the uncertainty in those estimates.

Finally, it should be noted that the example applications presented in this paper do not take into consideration the uncertainty in the estimate of the ED_{50a}. For most experiments, the value of ED_{50a} is determined by curve fitting. The uncertainty in the estimate from such approaches can be statistically characterized. Because the case studies do not consider the uncertainty in the estimates they only partially capture the uncertainty in the risk estimates. As a result, the response estimates in the case studies should be viewed with caution.

The approach does not require detailed information on a compound's dose response relationship in test animals. Only two pieces of information are required: the NOAEL for the critical effect, and an estimate of the

ED_{50} in the same study. The approach does require probability density functions for the uncertainty factors.

In this manuscript, we use a reference distribution to characterize the uncertainty in the UF_A and UF_H. This distribution is based upon the values for the uncertainty factors historically used in setting the RfDs and the logical implications of the concepts used in setting uncertainty factors. It is recognized that it will be useful to develop empirically-based characterizations of uncertainty for each of the existing regulatory factors. The work presented by Baird *et al.*[8] is a start in this direction. In addition, we are currently developing such distributions as part of our ongoing research in uncertainty factors.[13–15]

However, because such distributions are not yet available, we believe that assessments based on reference distributions can prove useful in two ways. First, the reference distribution is a means of exploring the implications of the approaches used for setting RfDs on the uncertainty in the RfD values.[19,20] Second, such distributions allow evaluation of the relative magnitude of uncertainty in RfDs established with different numbers of uncertainty factors.

This approach can be useful in a number of ways. For example, if an exposure assessment indicates that individuals may receive exposures to doses in excess of the RfD, many risk managers regard such exposures as unacceptable.[21–23] This approach can be used to provide some insight on the magnitude of the effects. Such estimates may also be helpful in risk/risk tradeoffs or cost-benefit analyses. This approach may be particularly useful in comparing the risks of one substance relative to another. Finally, this approach may also be useful in evaluating the *a priori* likelihood that an epidemiology study would detect the occurrence of adverse effects in an exposed population. Epidemiology studies typically cannot detect increases in adverse effects that fall below a certain occurrence rate. The proposed model can be useful in estimating the probability that the occurrence of adverse effects would be high enough to be statistically detected by an epidemiology study.

5. CONCLUSIONS

This approach offers a method of evaluating noncarcinogenic risks associated with doses above the RfD, offering a number of advantages over the current system of hazard quotients. First, the approach is consistent with the current system for establishing RfDs as it uses the same system of uncertainty factors and toxicological endpoints. Second, the approach does not require the risk assessor to have data on or make assumptions about the shape of the dose response curve in humans nor is a particular mechanism assumed to determine the response. Finally, the model can serve as a framework for integrating the uncertainty in toxicological measurements with the uncertainty associated with extrapolating from animals to humans. However, the model uses a number of simplifying assumptions that are generally biased toward overestimating response rates. This bias should be taken into account when evaluating the model results. This approach along with other techniques such as categorical regression[24–26] may provide considerable insight into the risks from noncarcinogenic effects of chemicals in the human population at doses above the RfD.

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