APPLICATION OF QUANTITATIVE INFORMATION ON THE UNCERTAINTY IN THE RFD TO NONCARCINOGENIC RISK ASSESSMENTS

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ABSTRACT

Recent efforts to improve risk assessment methodologies have sought to provide a fuller representation of the variability and uncertainty in risk estimates in order to provide risk managers with a more complete description of risks. Recently, we and others (Swartout *et al.*, 1998; Price *et al.*, 1997; Slob and Pieters, 1997; Baird *et al.*, 1996) have proposed approaches to characterize the uncertainty in the reference dose, (RfD) a key component of the non-carcinogenic risk estimation process. The operational definition of the RfD as the "lower-bound" estimate of the NOAEL in a sensitive human subpopulation ($NOAEL_{HS}$) is used along with information on the inter-chemical variation in ratios associated with the uncertainty factors used in setting the RfD to characterize the uncertainty in the $NOAEL_{HS}$ (Swartout *et al.*, 1998). This paper presents a description of how information on the uncertainty in the $NOAEL_{HS}$ can be used to characterize the uncertainty and variability in estimates of Hazard Quotients (HQ) and Hazard Indices (HI) for a population. The paper also explores the impact of using alternative approaches for defining inter-chemical variation in the ratios. The benefits of characterizing the uncertainty in noncancer toxicity estimates as well as limitations of the proposed approach are discussed. The analysis suggests four findings. First, the current method of estimating risks from mixtures of chemicals may overestimate the true HI when two or more compounds contribute significantly to the index. Second, the probability of a dose in excess of the RfD exceeding the $NOAEL_{HS}$ depends upon the number of UFs used in deriving the reference dose. Third, jointly assessing both the uncertainty and variability in exposure and the uncertainty in the estimate of the $NOAEL_{HS}$ can have a significant impact on the characterization of

noncarcinogenic risks. Finally, the findings remain generally consistent when various estimates of inter-chemical variation in ratios used.

KEY WORDS

Uncertainty, noncancer risk assessment, Monte Carlo, variability, reference dose, exposure

1.0 INTRODUCTION AND BACKGROUND

Environmental risk assessment is a field of pervasive uncertainty. Over the last ten years, risk analysts have begun to investigate the sources of uncertainty in risk assessment and their effect on risk estimates, especially uncertainties relating to exposure estimates (McKone and Bogen, 1992; Finley and Paustenbach, 1994; Thompson *et al.*, 1992; Price *et al.*, 1996; Baird, *et al.*, 1996). Recently, Swartout *et al.* (1998) have proposed a framework for evaluating non-carcinogenic risks. Under this framework, the RfD is defined as the lower confidence limit in an estimate of a minimum risk level. This minimum risk level is conceptually defined as the NOAEL in a sensitive human subpopulation ($NOAEL_{HS}$). The value of the $NOAEL_{HS}$ for a substance is estimated based on the application of a series of ratios of toxicological endpoints that convert or scale the reported NOAEL or LOAEL in the data for a compound to the $NOAEL_{HS}$. These ratios are associated with the uncertainty factors historically used in setting the RfD (Swartout *et al.*, 1998). This paper examines how quantitative representations of the uncertainty in a noncancer $NOAEL_{HS}$ (Swartout *et al.*, 1998; Price *et al.*, 1997) can be used, alone or in conjunction with uncertainty in exposure estimates, to quantitatively characterize the uncertainty in estimates of noncancer risks[1]. Two hypothetical case studies are presented in which quantitative estimates of the uncertainty in $NOAEL_{HS}$s are used to generate information on the uncertainty in noncancer risk characterizations. The results of these case studies are compared to results obtained using the RfD.

[1] Although the HQ is not really an estimate of risk (i.e., probability of effect), the term risk will be used in this paper as it is consistent with USEPA terminology.

The current system of evaluating noncarcinogenic risk is essentially a comparison of the estimated dose to the RfD (USEPA, 1989)[2]. Such a comparison is used by the risk manager to ascertain whether the exposure is above a dose which is unlikely to result in "adverse" or "deleterious" effects (a dose less than the RfD) or one judged to have some potential to cause an adverse effect (a dose greater than the RfD).

The comparison of the dose and the RfD is expressed in terms of a Hazard Quotient (HQ) (Stara, *et al.*, 1987). The HQ is defined as the ratio of the dose resulting from exposure to a single chemical to the RfD[3].

$$HQ_i = D_i/RfD_i \qquad \text{Eq. 1}$$

where D_i is the dose of chemical *i* and RfD_i is the RfD for chemical *i*. Under this system, an HQ that exceeds a value of 1.0 indicates that the estimated dose is greater than the RfD. The HQ ratio is designed to provide a common measure of relative risk across chemicals and exposure scenarios that is independent of the specific value of the RfD. This approach is intended to provide consistency for risk managers faced with evaluating exposures involving different chemicals with different toxicities. The approach also provides a useful basis for evaluating risks from exposure to mixtures of chemicals or from simultaneous exposure to multiple chemicals (USEPA, 1989; USEPA, 1986). Cumulative

[2] This paper will use the term dose to refer to dose rate (mg/kg-day).

[3] The RfD is expressed in terms of milligrams of chemical per kilogram body weight per day (mg/kg-day).

risks from exposure to multiple chemicals that elicit the same adverse effects and share a common mode of action are calculated using the Hazard Index (HI). The HI is calculated by Equation 2.

$$HI = \sum HQ_i = \sum D_i/RfD_i \qquad \text{Eq. 2}$$

where D_i is the dose of the *i*th chemical in the mixture and RfD_i is the RfD for the *i*th chemical. The advantage of this approach is that a single risk metric is developed for exposures to multiple chemicals. For example, the USEPA (1990) and several state agencies (MDEP, 1996; 58 N.J. Rev. Stat., 1997) have stated that all values of HI and HQ greater than 1.0 represent unacceptable levels of risk.

A number of researchers have identified limitations with the current system. These limitations include:

- the values of HQ and HI cannot be converted to quantitative estimates of the probability of adverse effects (Renwick and Walker, 1993; USEPA, 1993);

- there is no assurance that the risks associated with HI or HQ estimates exceeding a value of one will be the same for different chemicals (Renwick and Walker, 1993; USEPA, 1993);

- the combination of upper-bound estimates of risk (or, here, lower confidence limits of the estimate of NOAELs in sensitive populations (Swartout *et al.*, 1998) across multiple

chemicals) misrepresents the uncertainty in the resulting combination (Putzrath and Ginevan, 1991; Putzrath and Ginevan, 1994; Gaylor and Chen, 1996).

In fact, in its Guidelines for the Health Risk Assessment of Chemical Mixtures (USEPA, 1996), U.S. EPA recommended that the uncertainty in the toxicity assessment should be carried through to the risk characterization, stating:

> Nonetheless, if sufficient data are available to derive individual acceptable levels for a spectrum of effects ..., or variabilities of the acceptable levels are known, or if the acceptable levels are given as ranges ..., then the hazard index should be presented with corresponding estimates of variation or range.

As discussed above, the RfD can be viewed as the lower confidence limit on the estimate of the $NOAEL_{HS}$ for a chemical (Swartout *et al.*, 1998). The uncertainty in the $NOAEL_{HS}$ can be quantified using the current equation for RfD derivation and replacing the point estimates of the uncertainty factors with distributions. Probabilistic techniques are used to simulate the resulting distributions of $NOAEL_{HS}$s. These distributions of the $NOAEL_{HS}$s reflect the uncertainty that stems from the lack of complete knowledge as to the true (but unknown) value of the $NOAEL_{HS}$ for a chemical.

When distributions of $NOAEL_{HS}$s are used in the place of the RfD in equations 1 and 2, the results are estimates of the probability that a dose of one chemical or a mixture of chemicals will be greater

than the true $NOAEL_{HS}$ for the chemical or mixture of chemicals. The estimates of dose in equations 1 and 2 can also be replaced with distributions that reflect the variability and uncertainty in the dose estimates (McKone and Bogen, 1992; Finley and Paustenbach, 1994; Thompson *et al.*, 1992; Price, *et al.*, 1992). Using Monte Carlo models of such equations, risk assessors can characterize the probability that portions of an exposed population are exposed at doses above the true but unknown $NOAEL_{HS}$ given the uncertainty in both the toxicity and dose components of the equation.

2.0 APPROACH

The impact of quantitative measures of dose-response uncertainty on the assessment of noncancer hazards was investigated using a series of case studies. These case studies were designed to assess the effect of applying probabilistic $NOAEL_{HS}$s on the following issues. First, how does the number of compounds, and the uncertainty in their individual HQs affect the uncertainty in the HI for a chemical mixture? Second, how is the uncertainty in an HI for an exposure to a mixture of chemicals affected by the number of uncertainty factors used in setting the RfDs for the compounds of the mixture RfD? And finally, how can information of the uncertainty in $NOAEL_{HS}$s be combined with information on variability and uncertainty in dose to characterize the uncertainty and variability in HQs?

The input variables for the case studies are displayed in Table I. A single "reference" distribution was used to represent each uncertainty, as proposed by Swartout et al. (1998). This three-parameter

lognormal distribution has a mean of 0.335, standard deviation of 0.3765 (both expressed as the logarithm to the base 10), and offset value of one. Further discussion of the basis for the reference distribution is provided by Swartout *et al.* (1998). The simulations were run in a Microsoft Excel spreadsheet (v 5.0, Microsoft™ Corporation, 1994) with the @RISK™ add-in (v 3.0, Palisade Corporation, 1994). The number of iterations was selected to achieve stability of ± 3% in the 97.5th percentile of the input distributions using Latin Hypercube sampling. For all cases except case 1.3, stability was reached at 10,000 iterations, while case 1.3 required 15,000 iterations.

3.0 CASE STUDIES

The uncertainty in the estimate of the $NOAEL_{HS}$ is a function of the number of uncertainty factors used in its derivation (Swartout *et al.*, 1998). As a result, compounds with the same RfDs but different numbers of uncertainty factors will have different uncertainty distributions for the $NOAEL_{HS}$. To explore this issue, Case Study 1 considers mixtures of chemicals with RfDs derived using varying numbers of uncertainty factors. In this paper an RfD established with a smaller number of uncertainty factor will be referred to as more "certain" than an RfD with a larger number of uncertainty factors.

Recent trends in risk assessment have been to move toward the quantitative assessment of uncertainty and variability (Price *et al.*, 1996; USEPA, 1992; USEPA, 1995; Frey, 1993; Bogen, 1995; Hoffman and Hammond, 1994). The availability of probabilistic $NOAEL_{HS}$s allows the joint analysis of variability in dose and uncertainty in dose and toxicity. Case 2 investigates the application of

probabilistic $NOAEL_{HS}$s to a distribution of HQs when confidence limits are specified for the distribution of doses.

Uncertainty in the HQs was estimated by substituting distributions for the UFs used in deriving each RfD; the resulting quantity is the uncertainty distribution for the $NOAEL_{HS}$ and was calculated as:

$$NOAEL_{HSi} = \frac{NOAEL_i}{\Pi UF_j} \qquad \text{Eq. 3}$$

where $NOAEL_i$ is the NOAEL for the ith chemical each UF_j is represented by a distribution.

Case I. Calculation of HIs for Chemical Mixtures Using Uncertainty Distributions of $NOAEL_{HS}$ and Point Estimates of Dose

In this case study a series of examples, Cases 1.1 to 1.3, examine the effect of probabilistic $NOAEL_{HS}$s on estimates of noncancer risk from exposure to multiple chemicals presumed to act by the same mechanism. Case 1.1 consists of mixtures in which the individual constituents, each with RfDs derived using the same number of UFs, contribute equally to the overall HI (i.e., HQs for all constituents are equal). Case 1.2 consists of a mixture in which a single constituent dominates the HI (the HQ for one chemical exceeds the HQs for the remaining constituents), but where the RfDs are again derived using the same number of UFs. Finally, Case 1.3 consists of mixtures in which different numbers of UFs are used in the derivation of RfDs in the mixture (*i.e.*, the RfD for the first constituent uses one UF while the RfD for another uses more than one). These three cases show how

the information on the uncertainty in the $NOAEL_{HS}$ can provide insight to risk managers on which constituents are of primary concern.

Case 1.1

Case 1.1 examines two mixtures (1 and 2) composed of two and five chemicals, respectively. The values of D_i and RfD_i (Eq. 2) components were defined such that summing across the HQs for each of the mixtures results in an HI of 1.0. In all three mixtures, the HQs for the individual constituents are equal. For example, in Mixture 1, each of 2 constituents has an HQ of 0.5; in Mixture 2, each of 5 constituents has an HQ of 0.2.

Figure 1 shows the distributions of uncertainty in the HIs for the three mixtures, using a box-and-whiskers style representation. This graph presents the mean and 2.5th, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th}, and 97.5th percentiles. The graph depicts the uncertainty in the HQs for each of the chemicals. This uncertainty can be thought of as the probability of the dose D_i exceeding the $NOAEL_{HS}$. A distribution for the HQ for a single chemical is also provided for comparison. For all three of the distributions, there is less than 2.5% probability that the HI exceeds 1.0 (see Figure 1) with the given number of model iterations. Summing HQs across greater numbers of chemicals (all with equivalent point estimates of HQs) results in greater disparity between the point estimate HI and the distribution of HIs. In Mixture 1, for example, the 97.5th percentile HI resulting from the stochastic combination of HQs is 0.5. For Mixture 2, the 97.5th percentile HI is only 0.4. As the number of constituents in

the mixture increases, the upper end HI continues to decrease, since the joint probability of selecting upper-bound HQs (from the tails of the distributions) for all chemicals is smaller.

Case 1.2

Case 1.2 examines a mixture where several constituents contribute to a total HI, but the contribution of one constituent is dominant. In Mixture 3, the HQ for Chemical A is 0.5 and the HQ for each of the remaining chemicals (B - E) is 0.125. As shown in Figure 1, the uncertainty distribution for this mixture has a 97.5th percentile of 0.5. Thus, where one chemical dominated the HI, the upper confidence limit of the estimate of the HI was increased.

Case 1.3

The results given in Case 1.2 are based on constituents with RfDs that are derived using two UFs. When RfDs for mixture constituents have varying levels of certainty (that is, different numbers of uncertainty factors), there can be a change in both location and shape of the distributions of HIs.

Case 1.3 demonstrates that the chemical with fewer uncertainty factors will contribute more to the HI when the mixture constituents have RfDs of varying certainty. Mixture 4 is composed of three chemicals, each having HQs of one. The RfD for Chemical A is derived using only one UF. The RfD for Chemical B is derived using two UFs. Figure 3 shows the distributions of HQs that result from

a Monte Carlo simulation of the uncertainty in the $NOAEL_{HSS}$ for each compound. As the figure shows, the HI is dominated by the contribution from Chemical A. Although the point estimate HQ for each chemical is 1.0, the distribution of HQs for Chemical A is greater than that for Chemical B. In fact, the 95th percentile of the distribution for Chemical A is 1.0, while the distribution for Chemical B does not reach 1.0 until above the 97.5th percentile.

For chemicals whose RfDs include more than two UFs, the disparity can be even greater. Figure 2 also shows the distributions of HQs of two chemicals for (Mixture 5). The RfD for Chemical A incorporates only one UF, while the RfD for Chemical B is based on three UFs. This figure illustrates how the addition of more factors reduces the importance of the less certain chemical in the determination of the total HI for the mixture. Table II summarizes the results of Case 1.

Case 2. Incorporation of Uncertainty in $NOAEL_{HS}$ and Uncertainty in Doses into Noncancer Risk Estimates

Case 2.1

Case Study 2.1 examines the impact of using a probabilistic $NOAEL_{HS}$ in the noncancer risk characterization associated with a distribution of doses representing the uncertainty in the dose to a randomly selected individual from an exposed population. The distribution of HQs for the randomly selected individual is first calculated by applying the RfD to the distribution of dose rates. The result,

shown in Figure 3, is that there is 5% probability that the randomly selected individual has an HQ greater than 1.0. A second distribution of HQs is calculated from a Monte Carlo model of equation 1, where the distribution of doses and $NOAEL_{HS}$s were based on the uncertainty in the dose to an individual and the uncertainty in the $NOAEL_{HS}$. In this case, the fraction of the model runs showing HQs greater than 1.0 is less than 2.5%.

This finding, however, must be interpreted carefully. The result of this case study is an expression of the probability that a *randomly selected* individual has an HQ greater than one. This should not be interpreted to mean that an individual at the 97.5th percentile of the dose distribution has an HQ of 1.0. What the analysis demonstrates is that the consideration of the uncertainty in the $NOAEL_{HS}$ results in a reduction in the estimate of the HQ for randomly selected individuals from an exposed population.

Case 2.2

In Case 2.2 the uncertainty associated with the $NOAEL_{HS}$ is combined with the uncertainty in dose by means of a Monte Carlo model of the total uncertainty in the HQ for various percentiles of a dose distribution for an exposed population. Unlike Case 3.1, the distribution of doses received by a population is expressed in terms of both variability and uncertainty. In this example both the dose and the uncertainty distributions were assumed to be lognormal, with geometric mean, geometric

standard deviation of 0.007, 2.3 (dose) and 1.0, 5.0 (uncertainty in dose). A hypothetical chemical was postulated with animal NOAEL of 2.7 mg/kg-day and RfD derived with two uncertainty factors.

The uncertainty and variability associated with the HQ distribution is assessed in two ways. First, the analysis is conducted using the point-estimate RfD, resulting in a two-dimensional distribution representing both variability and uncertainty in the dose component of the HQ[4]. The distribution of interindividual variability in exposure in this example is the same as the uncertainty in the dose to a randomly selected individual used for Case 3.1; thus, an HQ of one occurs at the median estimate of the uncertainty of the dose to individuals in the 95th percentile of exposure (variability). The second assessment takes into consideration the uncertainty in the $NOAEL_{HS}$, resulting in a two-dimensional distribution representing variability in exposure and uncertainty in both the exposure and toxicity components of the HQ.

The probabilistic $NOAEL_{HS}$ was applied in the following manner. It was assumed that the total uncertainty in the estimate of the HI for each of the percentiles is a function of the uncertainty in the $NOAEL_{HS}$ and the uncertainty in the dose for that percentile. A Monte Carlo analysis was performed that calculated the total uncertainty in the HQs for each percentile of the exposed population using

[4] In order to simplify the analysis, we have assumed that the degree of uncertainty is constant across all percentiles of the exposed population. A more thorough analysis could address the uncertainty in the parameters of the dose distribution through the use of a nested-loop Monte Carlo analysis (Hoffman and Hammond, 1994) however, this approach was not necessary for the purposes of this analysis.

the uncertainty distributions for the $NOAEL_{HS}$ and the uncertainty distribution for the dose of each percentile of the exposed populations. This resulted in the generation of a two-dimensional model of HQs for the exposed population.

Figure 4 presents these two characterizations of the distributions of HQs. The first is the estimate of the HQs that result from the application of the point-estimate RfD to the two-dimensional (variability and uncertainty) model of doses. The second reflects the combined uncertainty in both the $NOAEL_{HS}$ and the variable dose-rate estimates. In both cases the outer two curves can be considered to represent upper and lower 95% confidence limits (UCL and LCL) of the distribution of HQs for the exposed population. The middle curves represent the median estimates, that is, estimates that have an equal probability of under-estimating or over-estimating the true value of the HQs for the population. In the first example, where the RfD is used, the median distribution indicates that 5% of the population has HQs equal to or greater than 1.0. However, the UCL on this distribution suggests that 95% of the population could have an HQ of 1.0 or greater.

The second example gives a different result. As Figure 4 shows, the curves for the second example are shifted downward, and, as expected, the uncertainty bands are expanded. In this analysis, the 95th percentile of the median distribution is much less than one (0.1). Further, the UCL on the distribution indicates that 30% of the population has an HQ equal to or greater than 1.0.

4.0 DISCUSSION

The use of probabilistic $NOAEL_{HSS}$ provides a number of insights into the assessment of noncarcinogenic risks. The example in Case 1.1 (Fig 1.) demonstrates that the current methodologies used to evaluate mixtures have an inherent conservative bias. When the HQs for two or more chemicals in a mixture make important contributions to the HI for the mixture, there is a potential to overestimate risk by a factor of two or more. This occurs because there is a very low probability that the true $NOAEL_{HS}$ for each of the compounds will be as low as the estimates of the RfD. The potential for overestimation increases with the number of compounds in the mixture.

Case 1.2 (Fig. 1) demonstrates two points. First, it is evident that the point-estimate approach to characterizing the HI of a mixture may provide a reasonable measure of hazard for mixtures where one constituent dominates the point-estimate HI. Second, the HI distribution will likely reflect the distribution for the dominant constituent *unless the RfD for one constituent is more certain than the others.*

As shown in Case 1.3 (Fig. 2), where RfDs may vary in the certainty of their derivation and all other factors are equal, the chemical with the more certain RfD will dominate the HI. This result implies that giving equal weight to HQs for chemicals with less uncertain RfDs and more uncertain RfDs can bias risk management decisions. (Finkel, 1990) noted that comparisons between outputs subject to hidden levels of conservatism can be precarious when "some real cases are less like the hypothetical

'worst cases' than others are". Such is the case in this example. The point estimate HQ for Chemical A and B indicates that they are equally hazardous. The probabilistic HQ assessment, however, suggests that Chemical B contributes far less to the combined hazard in both mixtures (Mixtures 5-6) than does Chemical A. While current U.S. EPA guidance recommends that the uncertainty in toxicity values be discussed qualitatively in risk assessment (Renwick and Walker, 1993), that guidance does not give risk managers sufficient information to evaluate the magnitude of the uncertainty or to acknowledge the uncertainty in making decisions regarding remediation. With the approach presented in Case 1.3, a risk manager is given additional information suggesting that in both mixtures, Chemical A, whose RfD is most certain, poses a greater hazard than Chemical B at the doses modeled.

Case 2 shows how information on the uncertainty in the $NOAEL_{HS}$ can be directly incorporated into a two-dimensional uncertainty analysis. Further, this example (Fig. 4) provides a visual perspective on both sources of uncertainty in the HQ (exposure and toxicity) as well as the magnitude and direction of uncertainty in the $NOAEL_{HS}$. This analysis is perhaps the most significant in this paper. The criterion for concern for non-carcinogenic effects is the probability that an individual at a site will receive a dose that has some potential for causing adverse effects. Traditionally this has been defined as doses that are more than the RfDs for the relevant compounds ($HQ \geq 1$). In Swartout et al. (1998), the RfD was defined as a lower bound estimate of the $NOAEL_{HS}$ associated with any given chemical exposure. This suggests that a more useful measure of the potential for noncarcinogenic risk is the probability that an individual will receive a dose of a chemical (or mixture of chemicals) that is greater

than the actual $NOAEL_{HS}$ for the compound (or mixture) in the sensitive population. This probability is determined by both the uncertainty in the individual's dose and the uncertainty in the $NOAEL_{HS}$. The characterization of the uncertainty in the $NOAEL_{HS}$, and the combination of this uncertainty with uncertainty and variation in dose estimates presented in this study are steps in characterizing that probability. Using the approaches outlined in this paper, risk assessors can provide managers with estimates of the probability that exposed individuals or fractions of exposed populations will have doses more than the $NOAEL_{HS}$s.

The foregoing results were derived using an uncertainty distribution for UF that is largely based on a specific interpretation of the probabilistic nature of uncertainty factors and not on empirical or mechanistic relationships (Swartout *et al.*, 1998). As a result, the above are relevant only in the context of probabilistic inferences arising from the application of the existing RfD methodology and do not necessarily have biological significance. Furthermore, the conclusions apply only in those situations where the full 10-fold default uncertainty factors are used in the derivation of the RfD. Situations of reduced uncertainty, in which uncertainty factors less than the 10-fold default are used, require the use of modified reference distributions (Swartout *et al.*, 1998).

Recently, Baird *et al.*, 1996; Swartout *et al.* (1997), Schmidt, *et al.*, (1997); and Slob and Pieters (1997) have proposed alternative uncertainty distributions for one or more uncertainty factors. Certain of these factors are based on empirical data. In order to evaluate the effect of alternative distributions on the analysis presented herein, these preliminary uncertainty distributions were used

in Case 1.3, Mixture 5 and the results compared with those observed with the reference uncertainty distribution. Uncertainty factors for interindividual variability, interspecies extrapolation, and subchronic-to-chronic extrapolation were included in the comparison. Since both (Baird *et al.*, 1996 and Schmidt *et al.*, 1997) presented species-specific interspecies distributions, the rat was selected as the test species for the hypothetical compounds.

Table III shows a comparison of the median and 95th percentile HQs and HIs resulting from the use of the reference and alternative uncertainty distributions. As the table demonstrates, where several uncertainty distributions combine (e.g., Chemical B), the results can vary depending upon the uncertainty distribution used. For example, the 95th percentile HQ for Chemical B is 0.15 using the Slob and Pieters (1997) distributions, but is estimated to be 0.75 using the Baird et al. (1996) distributions. Despite this difference, the qualitative results remain consistent within a given set of distributions; Chemical A presents a greater hazard than Chemical B despite their nominally equal point estimate HQ. These results, based on a limited set of alternative distributions, suggest that different quantitative and qualitative interpretations can arise from a alternative uncertainty distributions. There is no clear indication, however, of the eventual impact of data-derived distributions on the interpretation of HQ distributions, either in magnitude or direction.

5.0 CONCLUSIONS

This paper demonstrates how the uncertainty in the $NOAEL_{HS}$ can be incorporated into noncancer risk assessment. The example analyses presented herein show that quantitative uncertainty analysis can lead to risk management decisions that differ from decisions based on point estimates of hazard. In addition, the analysis shows that the uncertainty in the $NOAEL_{HS}$ can be quantitatively incorporated into a two-dimensional analysis of variability and uncertainty to provide information on the significant sources of uncertainty in noncancer hazard estimates.

The approach to noncancer risk assessment presented here is limited in that it is not designed to address the probability of effects at doses exceeding the RfD or $NOAEL_{HS}$. Unlike cancer risk assessment, current noncancer risk assessment is centered around an evaluation of whether an estimated exposure exceeds a "bright line" criterion (HI or HQ > 1.0). Thus, the approach presented here does not differ from current methods of assessing noncancer risks in this regard, but rather, provides a means of characterizing the probability of exceeding the" bright line" test.

This analysis shows that the quantitative assessment of uncertainty in RfDs can provide additional information which may be of use in risk management decision making. One example is the finding in Case 1 that an HI in excess of 1.0 for certain mixtures may be associated with lower potential for risk than a finding of an HQ of less than 1.0 for single compounds. An additional example is the potential to use information on the uncertainty in the HI or HQ in risk-risk comparisons. For

example, if a risk manager was comparing risks of radiation and the noncancer risks from chemicals it may be appropriate to use the most likely estimate of HQ or HI in comparison since the estimates of radiation risks are best estimates and not upper bounds. The proposed approach relies upon the current system of UFs and thus does not require any additional toxicological information. As a result, we believe that the approach can aid risk assessors in achieving the goal of the Guidance for Risk Characterization of "... explaining confidence in each assessment by clearly delineating strengths, uncertainties, and assumptions, along with the impacts of these factors" (USEPA, 1995).

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Figure 1. Uncertainty in Hazard Quotients or Hazard Indices
Case Studies 1.1 and 1.2

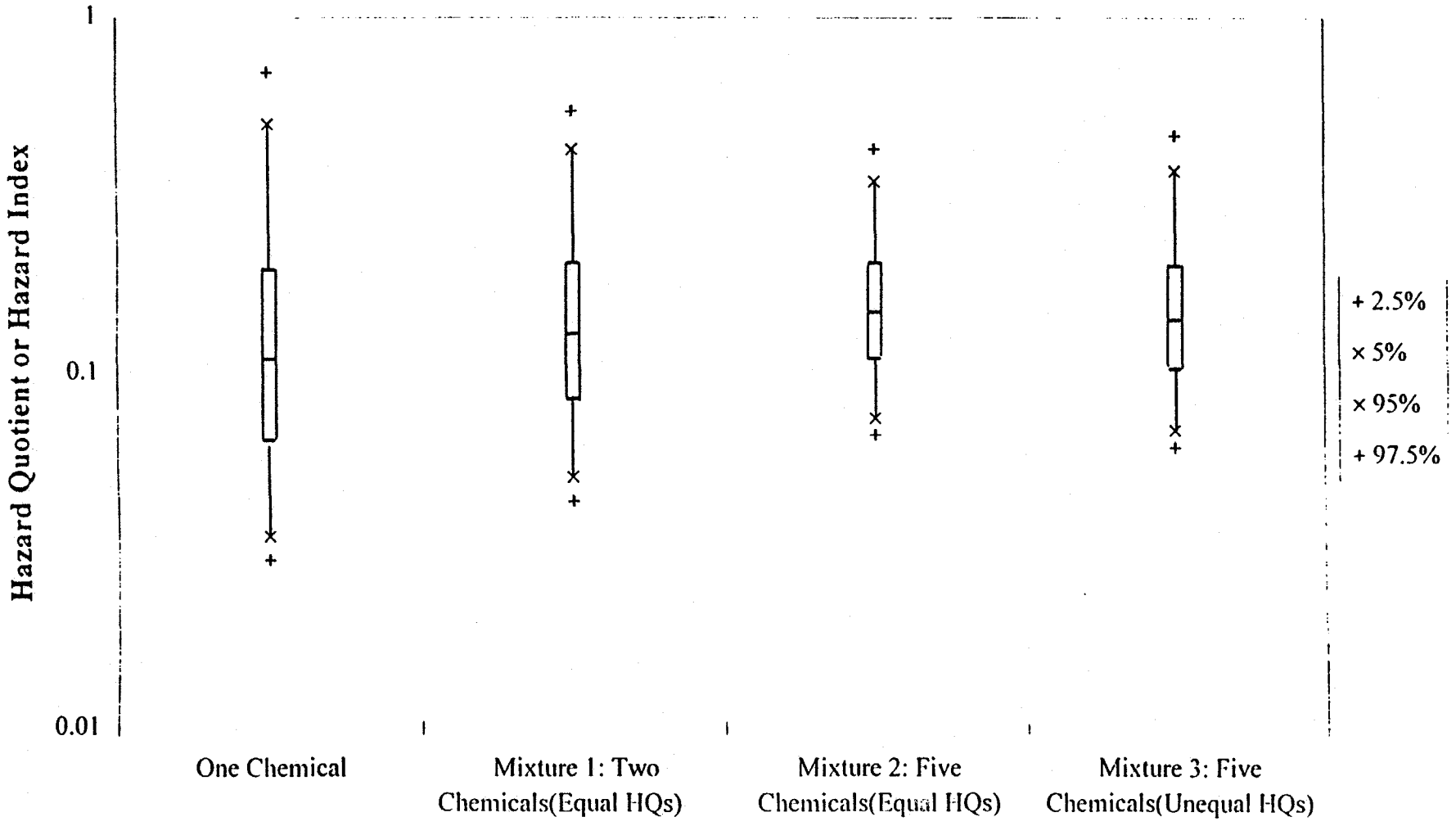

Figure 2. Uncertainty in Hazard Quotients and Hazard Indices
Case Study 1.3

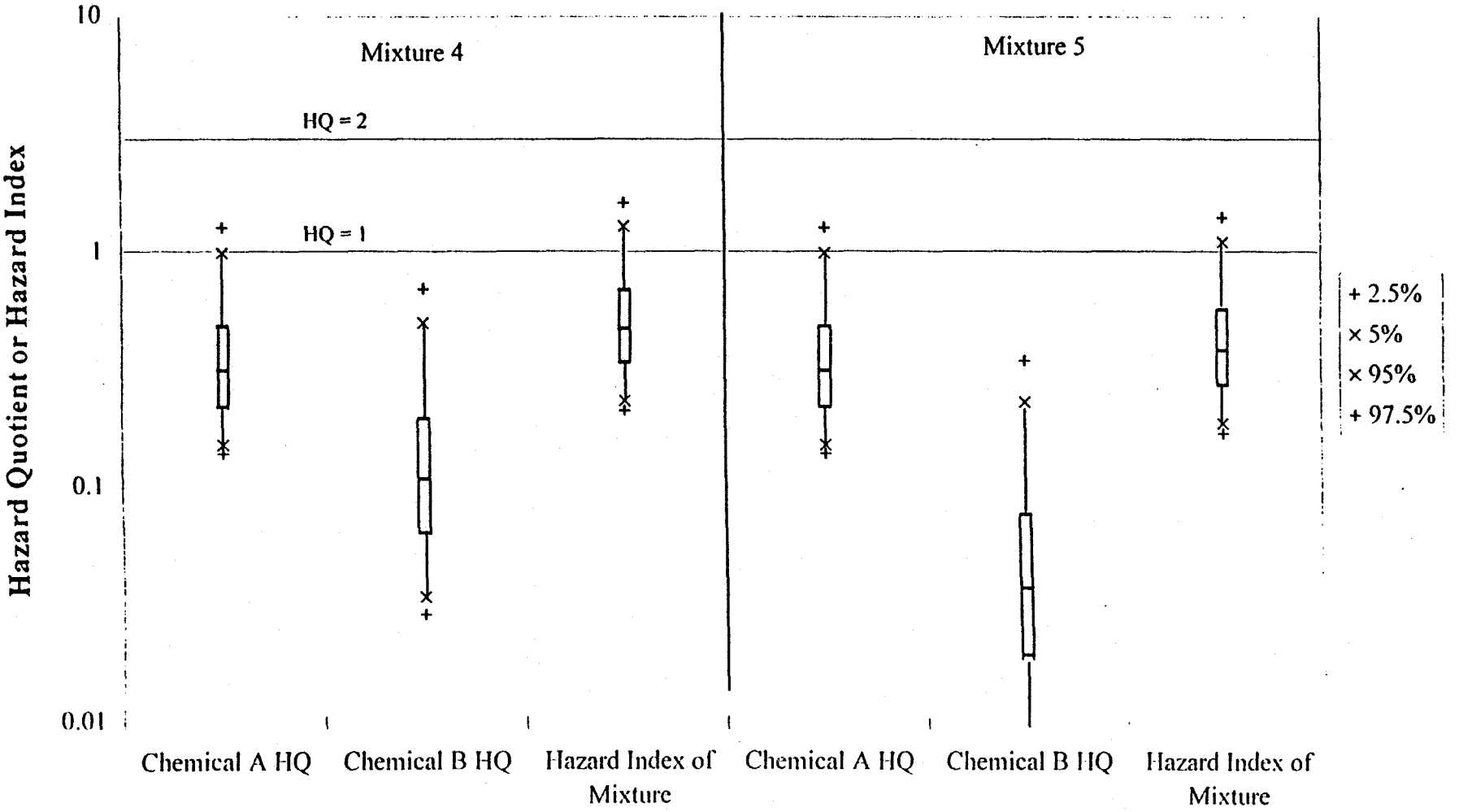

Figure 3. Uncertainty in Hazard Quotients for Randomly Selected Individual
Case Study 2.1

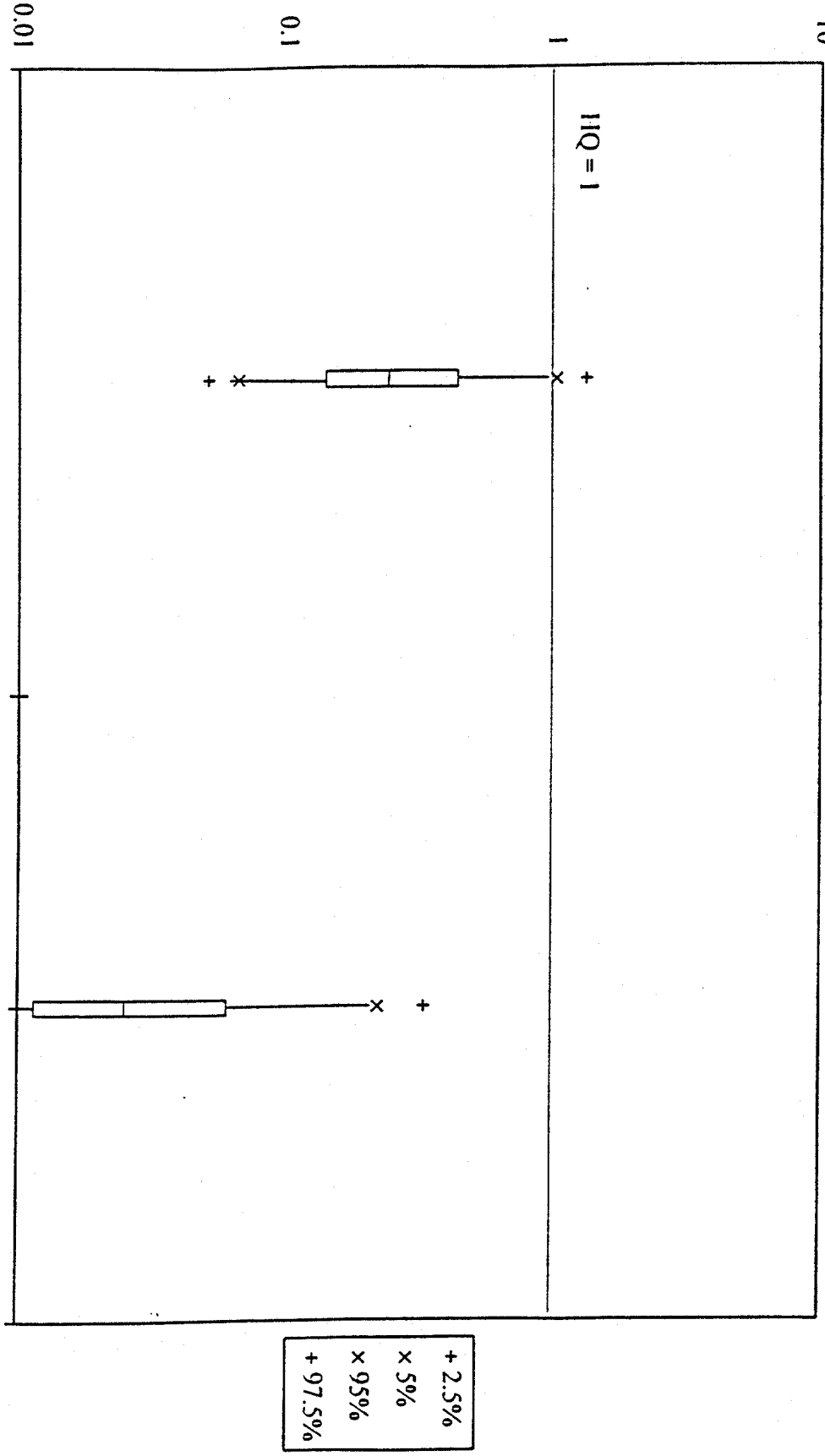

Figure 4. Two-Dimensional Model of Variability and Uncertainty in Hazard Quotients
Case Study 2.2

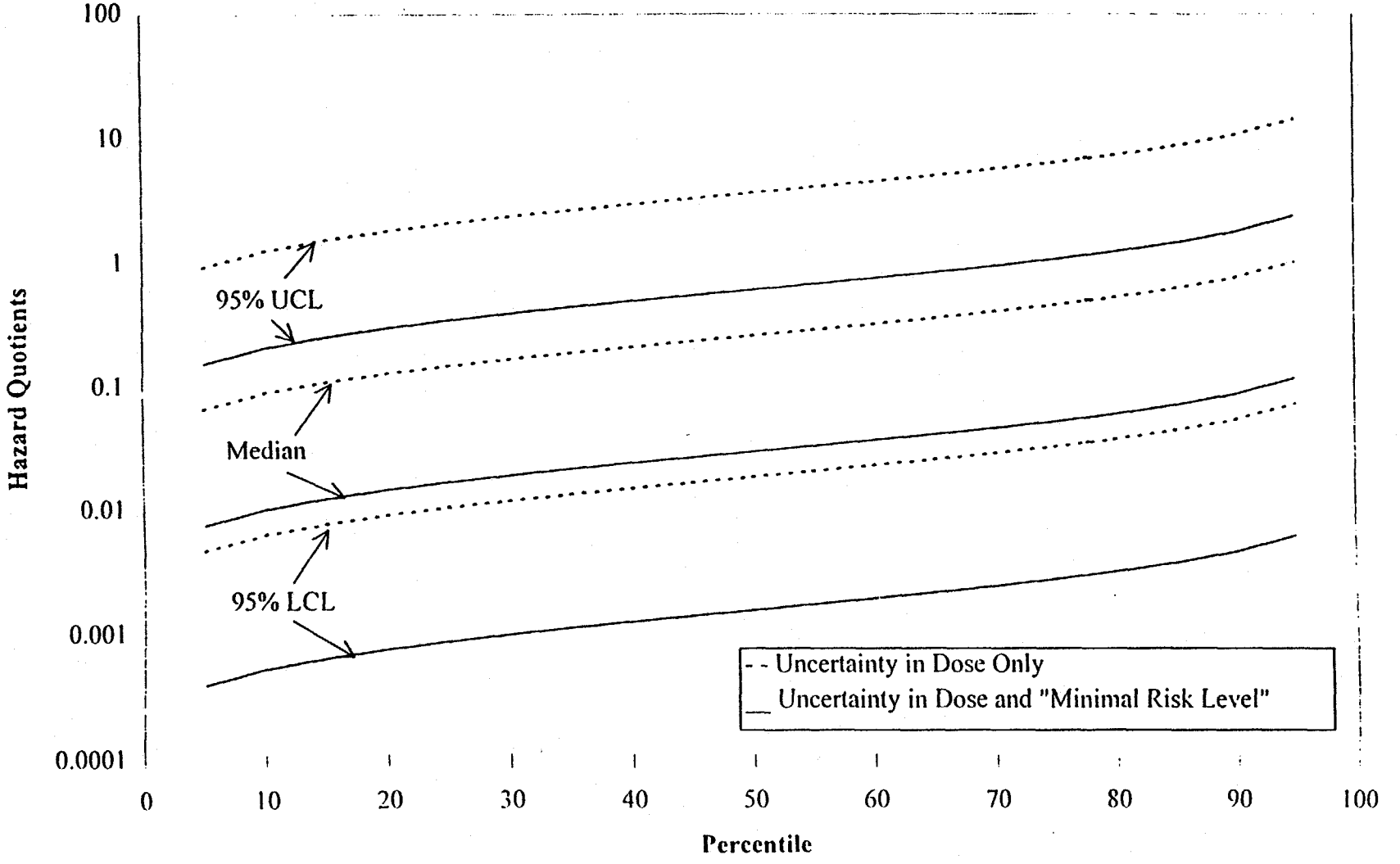

Table I
Input Variables for Case Studies[a,b]

Example	Chemical	Total UF(s) used	Point Estimate RfD (mg/kg-d)	Exposure (mg/kg-d)	Nominal HQ
Case 1.1: Mixtures of Compounds with Equal Contribution to HI					
Mixture 1	A	2	1	0.5	0.5
	B	2	1	0.5	0.5
Mixture 2	A	2	1	0.2	0.2
	B	2	1	0.2	0.2
	C	2	1	0.2	0.2
	D	2	1	0.2	0.2
	E	2	1	0.2	0.2
Case 1.2: Mixtures Where One Compound Dominates the HI					
Mixture 3	A	2	1	0.5	0.5
	B	2	1	0.1	0.125
	C	2	1	0.1	0.125
	D	2	1	0.1	0.125
	E	2	1	0.1	0.125
Case 1.3: Mixture Components with Different UFs and Same HQs					
Mixture 4	A	1	10	10	1
	B	2	1	1	1
Mixture 5	A	1	10	10	1
	B	3	0.1	0.1	1

a. Additivity of HQs to calculate HI implies that all contributing constituents share a common mode of action or elicit the same adverse effect.

b. NOAEL for each hypothetical chemical is equal to 100 mg/kg-day.

Table II
Comparison of Point Estimate with Median and 95th Percentile Values Derived from RfD Distributions

Substance	Total UF(s) used	Nominal Value	Median	95th Percentile
Case 1.1: Mixtures of Compounds with Equal Contribution to HI				
Mixture 1 HI	2	1	0.1	0.4
Mixture 2 HI	2	1	0.1	0.3
Case 1.2: Mixture Where One Compound Dominates the HI				
Mixture 3 HI	2	1	0.1	0.4
Case 1.3: Multiple Compounds with Different UFs and Same HQs				
Chemical A HQ	1	1	0.3	1
Chemical B HQ	2	1	0.1	0.5
Mixture 4 HI		2	0.5	1
Chemical A HQ	1	1	0.3	1
Chemical B HQ	3	1	0.04	0.2
Mixture 5 HI		2	0.4	1

Table III
Comparison of Case 1.3 Results Using Reference and Empirical Uncertainty Factor Distributions

	Median	95th Percentile
Chemical A HQ, Mixture 5		
Reference[a]	0.32	1
Empirical I[b]	0.27	1.1
Empirical II[c]	0.27	1.1
Empirical III[d]	0.40	0.8
Chemical B HQ, Mixture 5		
Reference	0.04	0.2
Empirical I	0.03	0.8
Empirical II	0.02	0.4
Empirical III	0.03	0.2
HI, Mixture 5		
Reference	0.38	1.1
Empirical I	0.37	1.6
Empirical II	0.34	1.3
Empirical III	0.45	0.83

a. Swartout et al., 1998

b. Baird et al., 1996

c. Swartout et al., 1997 Schmidt et al., 1997 and Baird et al., 1996