# A MONTE-CARLO APPROACH TO INCLUDING UNCERTAINTY IN REGULATORY RISK ANALYSIS: Reanalysis of DBCP Cancer Risk for Fresno County, California

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We shall briefly review the current approach to regualtory environmental heath risk analysis, focusing on the context of pesticides. We then offer a fundamental criticism of this approach, propose an alternative general approach based on Monte-Carlo simulation, and provide an example of its application in the area of cancer risk analysis for a pesticide groundwater contaminant.

## 1. The Regulatory Context

Regulatory risk analysis generally begins with an assessment of the extent to which certain population groups are exposed to a compound determined to have adverse health effects at some dose level. In the context of pesticide risk assessment in the context of EPA's "Rebuttable Presumption Against Registration" (RPAR) procedure, the general approach used involves a mixture of "averaging" and "worst-case" exposure descriptions, although operational definitions for these terms are rarely provided. For example, in setting chlorobenzilate residue tolerances the following were used: average crop consumption estimates, averaged dispersion estimates which assume that an entire projected pesti-

cide residue mass is distributed evenly throughout the entire U.S. crop to which the pesticide is applied, and "reasonable upper limit" occupational exposure estimates based on maxima of several sets of exposure measurement means (EPA, 1980a). In reviewing EPA's exposure assessment approach, a National Academy of Sciences committee concluded: "At present the position documents and supporting reports almost invariably violate [the principle of presenting unbiased exposure analyses]. Indications of ranges of uncertainty are rare . . . [and] generally present as estimates of exposure the single, upper-limit, 'worst case' values for each exposed group" (NAS, 1980).

For chronic toxicity endpoints other than oncogenesis and mutation, RPAR dose-response assessments are most often based on experimentally derived "No Observed Effect Levels (NOELs). It is assumed that for these endpoints the absence of any observed toxic response in a group of experimental animals at a given dose level indicates that no such response would have occurred even if the exposed group of animals were much larger than that actually used. That is, the assumption is made that there is a threshold in the dose-response relationship for that effect. Test results for at least two animal species are generally required to make a NOEL determination (EPA, 1982a). Human epidemiological data can also be used for this purpose, and positive human epidemiological findings will generally outweigh negative experimental test results. In the context of regulating environmental pesticide exposure levels, a "Maximum permissible exposure level" (MPI) for humans is derived from an experimental NOEL by dividing by standard weight (e.g., 70 kg) and by an appropriate safety factor (EPA, 1978). The safety factor is usually 100 but may be raised by a factor of from two to ten or

more in cases where there is very little toxicological data upon which to base a risk analysis. (E.g., in the context of regulating drinking water contamination, EPA sets ADIs using safety factors of 10, 100, or 1000 depending on the quality and quantity of available toxicological data in accordance with recent National Academy of Sciences recommendations (NAS, 1978).)

In practice, an MPI in an RPAR risk determination is combined with a "worst case" public or occupational exposure assessment to yield a corresponding "margin of safey" (MOS) defined as:

$$\text{MOS} = \frac{\text{MPI}}{(\text{Proposed Exposure Level})} \bullet$$

The MOS serves as a rough guide to exposure acceptability for the regulatory decisionmaker. For example, a MOS less than 1 generally is regarded as unacceptable, whereas a MOS between 1 and 50 may indicate that alternative regulatory strategies should be considered which might act to lessen prospective exposures.

Dose-response assessment in the context of regulating exposure to tumor-causing agents has been far more controversial than that for other types Of toxic response. EPA dose-response assessments for carcinogenicity have been based on the position that in a variety of regulatory contexts a "linear non-threshold" model is the mathematical model of choice for extrapolation of cancer risk at very low dose levels (EPA, 1976; EPA, 1979a; IRLG, 1979; EPA, 1980b; EPA, 1980c). A similar position is currently developing in regard to low-dose mutagenicity risk extrapolation (EPA, 1980d; NAS 1982). In the context of risk assessment for chemically induced tumors (in RPAR and other regulatory proceedings), the specific linear model used by EPA (Cancer Risk Assessment

Group, Office of Health and Environmental Assessment) is the "linearized multistage" model (Crump, 1981). This model treats lifetime increased cancer risk as the following function of dose:

$$A(d) = 1 - e^{-(q_1 d + q_2 d^2 + \ldots + q_k d^k)} ,$$

$$\text{where} \quad A(d) = \frac{P(d) - P(0)}{1 - P(0)} = \text{Abbot's Correction}$$

and where $q_i \geq 0$, $k \leq$ the number of experimental dose groups, and d = dose. Maximum likelihood procedures to estimate multistage parameters from dichotomous tumor response data have been developed (Guess and Crump, 1976, 1978a, 1978b; Guess et al., 1977; Crump et al., 1977; Crump, 1981). Using these procedures, maximum likelihood estimates of $q_i$ are obtained and then a 95% upper confidence limit of $q_1$ is calculated ($= \hat{q}_1^*$) consistent with $\hat{q}_j$, $j = 2,3,\ldots,k$. Increased low dose cancer risk is then calculated by the formula

$$A(d) = \hat{q}_1^* d ,$$

intended to represent "the most plausible upper limit" of the additional risk (Anderson, 1977; EPA, 1980c).

The point of the "linearized multistage" model, then, is to calculate a "maximum plausible" risk rather than a "most likley" risk. Maximum likelihood risk estimate's based on the "linearized multistage" model can be many orders of magnitude lower than those produced by the simpler one-hit model, depending on the nature of the data analyzed. However, 95% upper confidence risk estimates base on these two models will rarely differ by as much as an order of magnitude regardless of the underlying data (Crump, 1981). This is so because $\hat{q}_1$ is always allowed

to be equal to zero in this model, whereas its calculated upper confidence limit $\hat{q}_1^*$ will always be greater than zero and generate a linear term that predominates at low doses. radiation in many contexts.

The exposure and dose-response assessment methodologies discussed which are currently used in the RPAR risk analysis process suffer from a failure to incorporate any explicit consideration of uncertainty in the dose-response relationship that is selected for use in a final risk analysis. For the first class of toxic endpoints discussed, the response of interest is zero-response, for which the corresponding highest dose is extrapolated by dividing a no-observed effect level by a safety factor without regard to the statistical reliability of the NOEL. The use of generic safety factors itself precludes the explicit treatment of uncertainty in dose-response asssessment. The low-dose cancer risk extrapolation model used by EPA for pesticide and other chemical carcinogens or suspected carcinogens is explicitly designed to yield a "plausible worst case" dose-response relationship, despite the fact that the underlying "linearized multistage" model is quite capable of generating maximum likelihood functions and plausible representations of their associated uncertainty given the variability in the experimental tumor response data used to derive those functions. Although ranges of uncertainty may be included in exposure assessments, there is currently no formal incorporation of this information into risk analysis and subsequent decision-making procedures.

## 2. A Monte-Carlo Approach

We propose that all information regarding uncertainty or variabil-

ity in variables that feed into a risk aanalysis be explicity included in the formal analysis in a way that yields the best characterization possible of true "risk", i.e., in a way that produces a probabilistic assessment of forseeable harm. In the context of a pesticide risk analysis, a traditional risk assessment framework considers the various pathways which a given chemical can be transmitted through the environment resulting in human exposure, i.e., absorption at the principle body barriers such as lung, skin, or gut. The exposure process is controlled by the level at which a relevent environment is contaminated (c) and the absorption rate (a), which together determine the dose rate, whcih in turn, when properly integrated over time, yields the dose (d) to a given population. A dose-response relationship P(d) then determines the expected response conditional on the assumptions use to generate c, a, d, and P(d).

We would replace the above deterministic model with an analogous one which explicitly incorporates either random variability or a priori uncertainty or both. In particular, the variables above can be treated as non-negative random variables C, A, and D and P(d) can be treated as a stochastic function of a random variable to generate a treatment of risk itself as a random variable, i.e., to generate a likelihood distribution of levels of harm that characterize a given environmental risk. The steps involved in combining the inputs to get a response distribution is depicted in Figure 1, which expresses the following equations:

$$D = CA$$

$$F_D(d) = \int \int f_C(c)\, f_A(a)\, dc\, da$$

$$R = P(D)$$

where F and f are the cumulative distribution and probability density functions, respectively, of their subscripted variables and where P(d) is understood to be itself a function with uncertainty in its parameter set H. The analytic form of a "risk distribution" (more precisely, a probability density function for the magnitude of anticipated adverse health impact) can be quite intractable in this context, depending on the complexity of $f_C(c)$, $f_A(a)$, and $f_H(h)$. For example, if C and A could both be modeled as log-normal variables, then D would also be log-normal. Assume further that P(d) were a "one-hit" function, i.e., the simplest type of multistage model having only a linear parameter, and that this parameter, say Q, could also follows a log-normal distribution. It follows that

$$R = P(D) = P(CA) = G(T) = 1 - e^{-T}$$

where T is also a log-normally distributed variable.

In this case, we derive $F_R(r)$ as follows:

$$f_R(r) = f_T(G^{-1}(r))\frac{dG^{-1}(r)}{dr} ,$$

$$F_R(r) = \int_0^r \frac{1}{\sqrt{2\pi}\, s\,(1-u)\,\ln(\frac{1}{(1-u)})}\, e^{-1/2\left(\frac{\ln[\ln\frac{1}{(1-u)}] - m}{s}\right)}$$

where m and s are the logarithms of T's geometric. mean and standard deviation, respectively. Thus, in this case $f_R(r)$ is a simple transform of a log-normal density function.

In general, such derivations would not be so straightforward. We

have therefore employed a Monte-Carlo approach to the derivation of $F_R(r)$, the cumulative distribution of risk to a given population. Once again, a point on Fr indicates that the corresponding level of harm or a lesser level is anticipated to occur with the corresponding likelihood, given the variability and/or a priori uncertainty associated with the random inputs, and as such can represent either a population risk (a probability that a given fraction of a population will be affected) or an individual risk (a probability of facing a given probability of harm). If N is the size of a large exposed population, the number of induced cases $N_1$ would be less than or equal to N times $r_1$ with probability $F_R(r_1)$. The mathematical expectation of $N_1$ is simply N times the mean value of R. Thus, the distribution $F_R(r)$ allows one to make probability statements about either the size or the proportion of an exposed population which will respond.

In using the methodology described, care must be taken to delineate what portion of a derived $F_R(r)$ is due to parametric variability expected to be encountered "in the field" and what portion is due to a priori uncertainties incorporated into the analysis to reflect fundamental gaps in knowledge concerning the causal links between contamination, exposure and toxic response. These two sources of uncertainty can have very different implications to industrial or regulatory policy-makers for whom such an analysis would be carried out. Of course, the final risk distribution generated will reflect reality only to the degree that (a) the processes involved have been modeled accurately and (b) their stochasticity and uncertainties have been reasonably accounted for. The advantage of the approach, however, is that it allows the analyst to explicitly consider uncertainty in the health risks considered to the

extent feasible, in a way that can reflect both natural variabilities in contamination, exposure and response and the uncertainties reasonbly implied by the use of basic inference bridges intrinsic to most health risk assessment, particularly regarding chronic health risks like those posed by environmental carcinogens.

## 3. Illustrative Application: Reappraisal of DBCP Cancer Risk

We have applied the described Monte-Carlo approach to a reassessment of cancer risk posed by the nematocide dibromochloropropane (DBCP) found in groundwater in Fresno County, California. DBCP was a popular and effective chemical used to control nematodes on a variety of important crops in the United States. In 1977 DBCP was implicated in the generation of adverse reproductive effects in male pesticide workers, and was subsequently banned for most agricultrual uses in the United States. DBCP was found to be carcinogenic in mice and rats in several studies conducted between 1972 and 1979. In this context, a water sampling program for the detection of DBCP contamination in the San Joaquin Valley and Southern California was initiated in 1979 and carried out over several years by the Water Hygiene group of the California Department of Health Services. In this survey all significant water sources serving the Fresno County population were assessed as it became apparent that many wells in this county were contaminated to some degree. This contamination data was used by Jackson et al. (1982) to perform an epidemiological comparison of DBCP drinking water contamination with mortality rates from selected cancers for that county between 1970 and 1979, a study which detected positive associations between cancer incidence and DBCP contamination level, particularly for stomach cancer

in males.

To obtain a comprehensive map of DBCP contamination of Fresno County drinking water, Jackson et al. combined DBCP contamination data from large and small water systems with information on annual flow rates in an algorithm to obtain a weighted average DBCP concentration value for each of 108 (1974/1980) census tracts in the county. In this study, however, census tracts were aggregated into only three DBCP exposure level categories: LOW (0-0.05 ppb), MEDIUM (0.05-1.0 ppb), and HIGH ($>$ 1.0 ppb). For our purposes it was desirable to reconstruct the entire distribution of DBCP concentration levels for all census tracts, which was possible through the gracious supply of the original analysis by Dr. Jackson, who used 1974 mid-census population figures. This resulted in an empirical concentration distribution function with 33 concentration categories ranging from 0.001 ppb (the original $\leq$0.005 ppb category was assigned the midpoint value 0.0025 ppb) to 8.4 ppb (mean = 0.792 ppb, s.d. = 1.65 ppb, median = 0.119 ppb, 95th %ile = 5.32 ppb, geom. mean = 0.0669 ppb, geom. s.d. = 15.66). Fresno County included 514,621 people as of the 1980 census, which differed little in total or by census tract from the 1974 mid-census figures.

In our analysis it is assumed, as in the Jackson et al. study, that the empirical contamination distribution derived reflects persistent concentration levels, although for our purposes it is only necessary that the distribution itself be persistent, rather than its geographic fixture. In the face of such a broad distribution of contamination, it was apparent that minor fluctuations in water consumption would have little effect on response. The standard assumption was made that water

intake averages 2 liters per 70 kg per day for the Fresno population, but that average consumption does vary log-normally such that 95% of the people drink between Multiplying concentration (in ppb = ug/liter) by weight-standardized intake (in liters/kg/day) yields a dose rate (in mg DBCP/kg/day). Dermal absorption of DBCP, e.g., during bathing, was not considered in this analysis.

For the purpose of this illustrative analysis the dose-response relationship for DBCP-induced tumorigenesis was assumed to follow a "one-hit" model, in accordance with the re-evaluation of DBCP carcinogenicity undertaken by EPA's Carcinogen Assessment Group (EPA, 1979b). The data selected to form the basis of the low-dose risk extrapolation were those from Hazelton, 1978, on DBCP-induced stomach, liver and kydney tumors in male rats. (This by itself constitutes a significant bias in that this was the most sensitive animal sex and species identified for DBCP's carcinogenic effect.) As in that analysis, the single most effective dose level was selected to generate a "best fit" (in this case "only fit") one-hit slope parameter (with units of risk/(mg/kg/day)) for each tumor type. EPA's 95% upper confidence slope parameter values were then used to derive reasonable forms of uncertainty in the slope parameters. Here two approaches were taken. The first approach was to assume that these parameters follow a 0-truncated normal distribution, with mean parameter equal to the best-fit value, in accordance with the theoretical expectation that the random variability in the linear parameter, which is constrained to be positive, asymptotically approaches normality when it can be assumed apriori to be different from 0 (Crump et al., 1977). This approach was used to derive results depicted in Figures 2-6. The second approach was to assume that the linear

parameter follows a log-normal distribution, with median equal to the best-fit value. This appraoch was used to derive the results shown in Figure 7, where "P(d)" is referred to now as Q(d) to emphasize the difference in approach. We note that when the full "linearized multistage" procedure is used to generate risk extrapolations, an attractive way to model the uncertainty in the linear term (which will, in fact, dominate the variability in the function P(d)) is to use the non-linearly transformed Chi-square distribution implied by the associated method used to generate confidence limits on risks and "safe" doses, namely

$$\ln(L_{max}) - \ln(L_{1-a}) = 0.5\, X^2_{1,1-2a}$$

where L is the likelihood function of P(d) described by Crump (1981) and a is the one-tailed significance level associated with $q_1^*$, the recalculated linear parameter in P(d). We also note that in the assessment Cited, the Carcinogen Assessment Group added together its upper 95% confidence levels, which is clearly inappropriate, (A reevaluation of DBCP carcinogenicity has just been completed by CAG, we understand.)

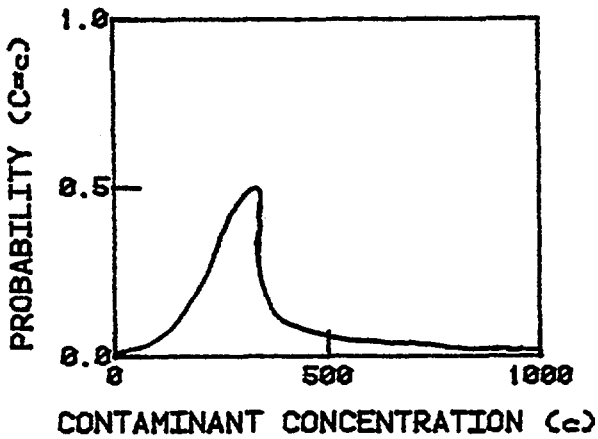
The results of our reappraisal of DBCP cancer risk using a Monte-Carlo approach are presented in Figures 2-7. Figures 2 and 7 reflect all uncertainty sources considered, as discussed above. In Figures 3-6, we have "filtered" various uncertainty sources to demonstrate their impact on total uncertainty. Note that the term "uncertainty" in the figures is meant to refer to both random variability and a priori uncertainty. In the present case, the variables C and A represent emprirical (in the case of A, semi-empirical) variability, whereas the selection of the analytic form of P(d) and the form of its stochasticity entails a

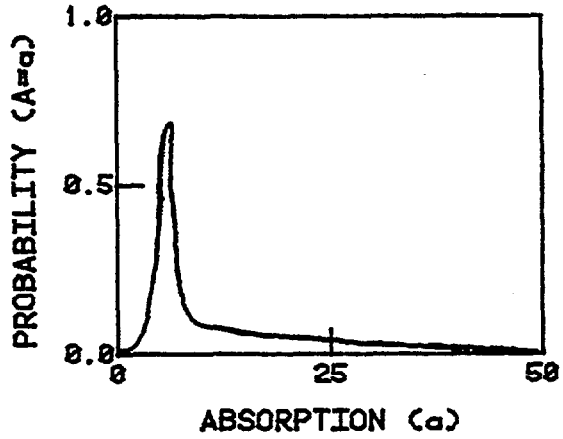
large degree of a priori uncertainty. But there is no reason why a reasonable representation of the latter uncertainty might not also be included in the analysis if it were felt that reliance on, e.g., only one low-dose extrapolation model is excessively unrealistic or scientifically unsound. A comparative appraisal of DBCP cancer risk prepared recently by Shell Oil Company appears to be in this vein (Shell, 1983). However, the Shell report presents only maximum likelihood risk values associated with DBCP exposure according to five different low-dose extrapolation models, and geometric means of these maximum likelihood values; they made no attempt to extend their analysis to the range of other uncertainties involved.

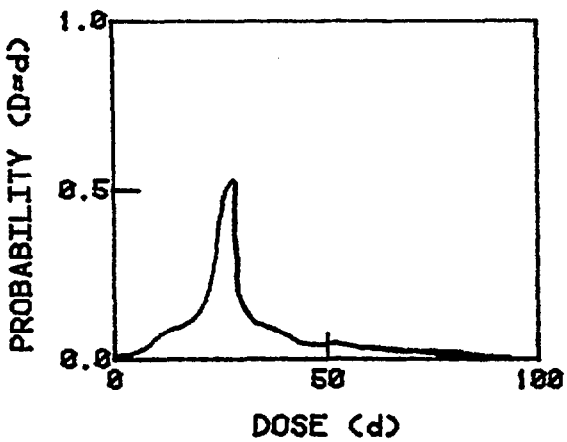
A summary of the results presented in Figures 2-7 appears in Figure 8. We feel that Figure 8 illustrates a way to present the output of Monte-Carlo risk analyses such as this which is readily communicable and useful to the regulatory decisionmaker as a summary of the technical appraisal of a given health risk and its associated uncertainty. The precise results can also be used for more in-depth policy analysis which would incorporate economic and other considerations bearing on risk management issues. In summary, we note a key feature of the DBCP risk analysis undertaken. The contamination distribution clearly dominates the variability present in the derived $F_R(r)$. This is to be expected since its 95% range spans close to 4 orders of magnitude--well above that for the absorption and dose-response variables. The skewness of the contamination distribution has a pronounced effect on the mean risk level, which is a clear demonstration that including uncertainty in risk analysis can significantly affect the analytic outcome even with respect to the simplest desriptors. This is intuitive on recalling that skewed

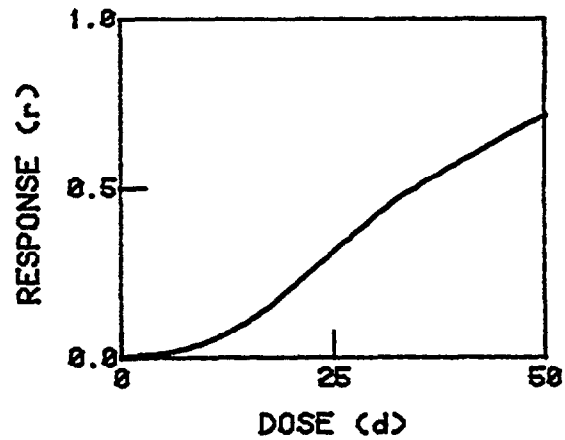
distributions (such as log-normal ditributions) become even more skewed when multiplied together, as we have done in this example, and that the greater the right-skewness a distribution has, the greater is the difference between its mean and median values.

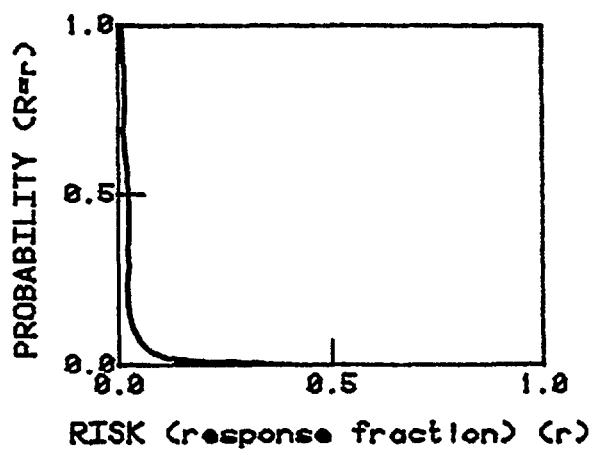
Figure 1: COMPONENTS OF PROBABILISTIC RISK ANALYSIS



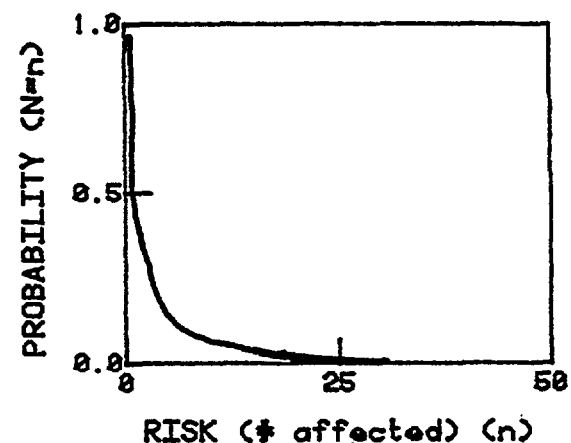
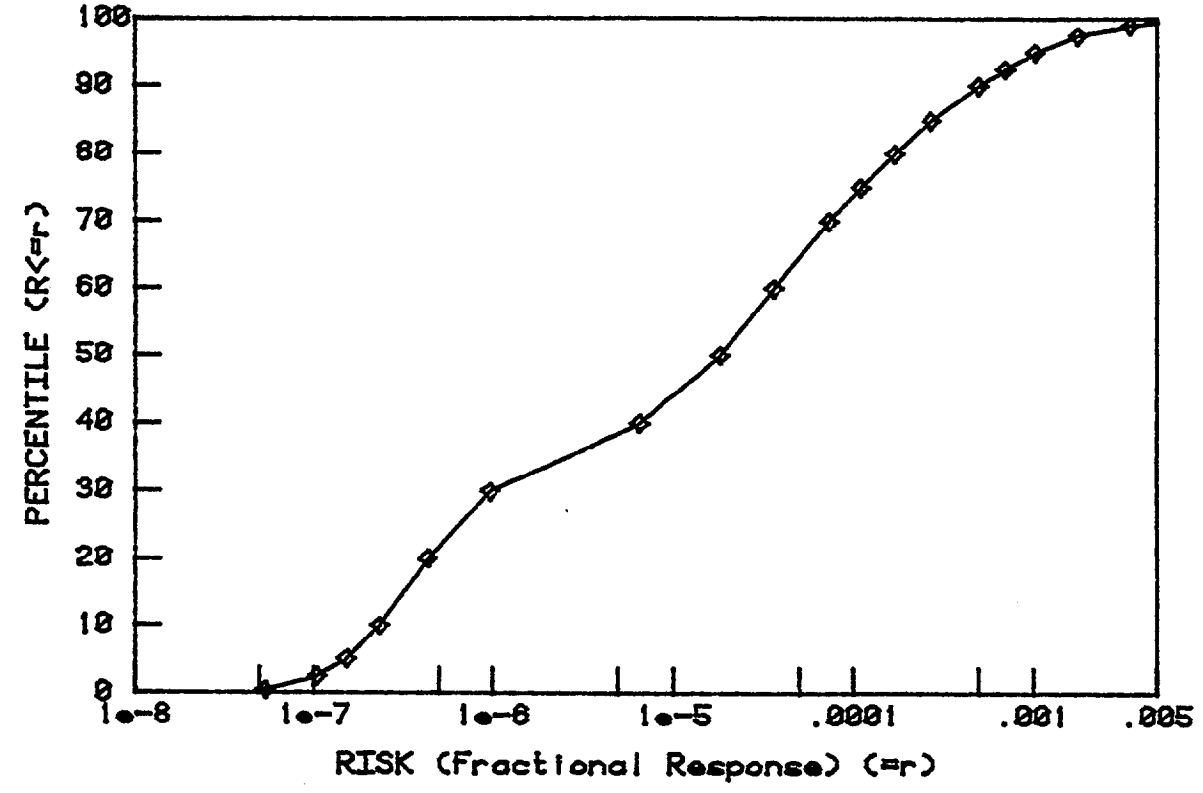



Figure 2: UNCERTAINTY IN c, a, and P(d)



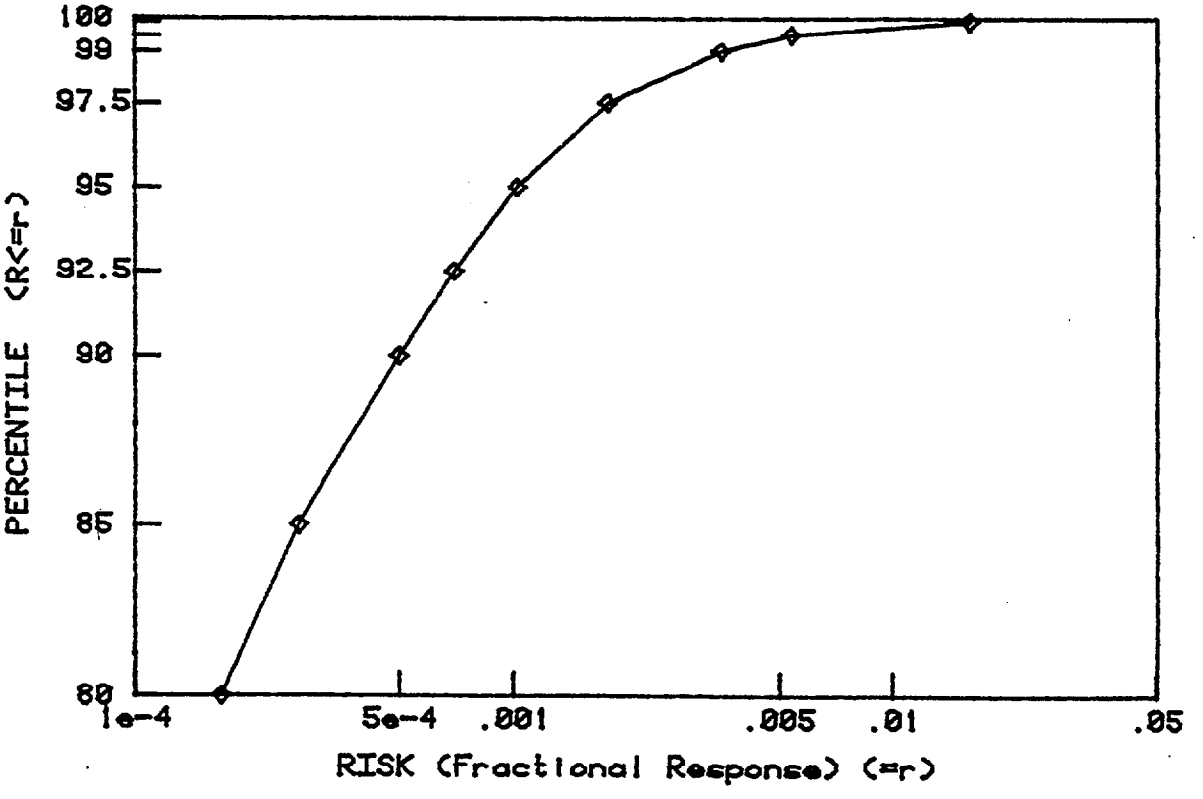
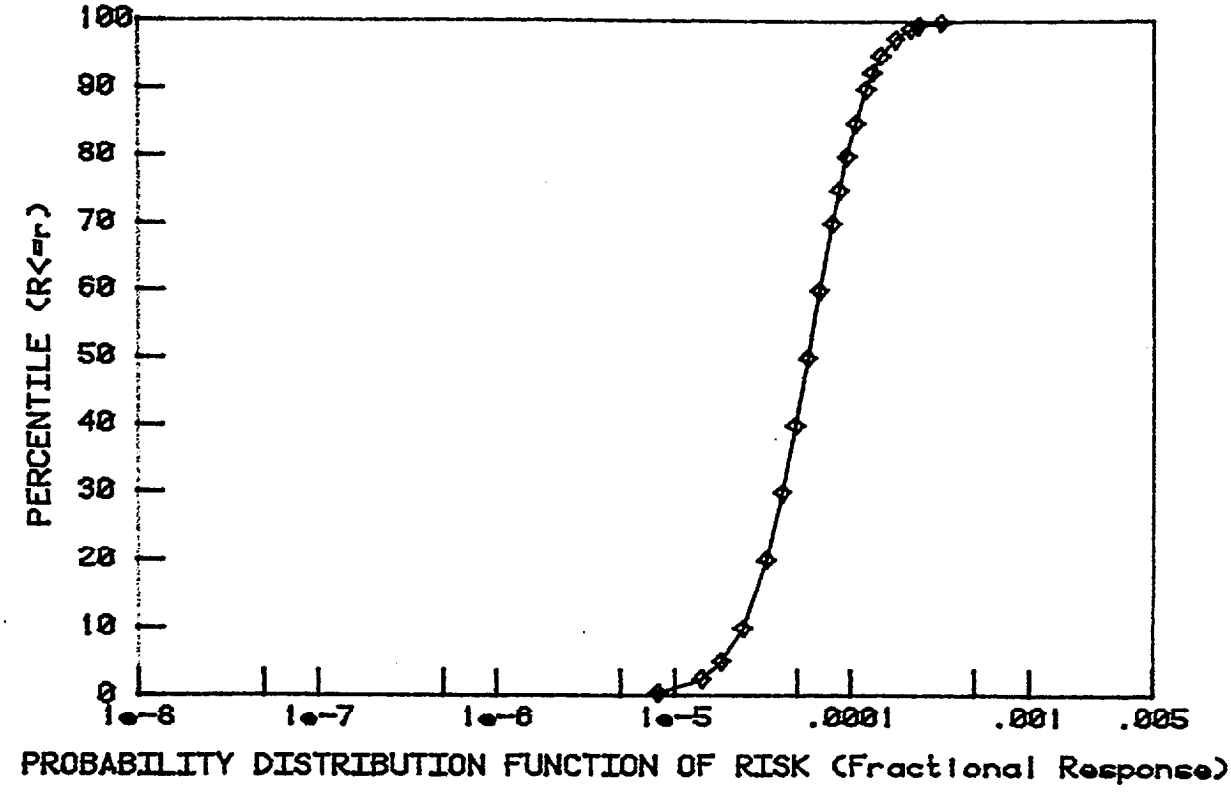



Figure 3: UNCERTAINTY IN a and P(d)



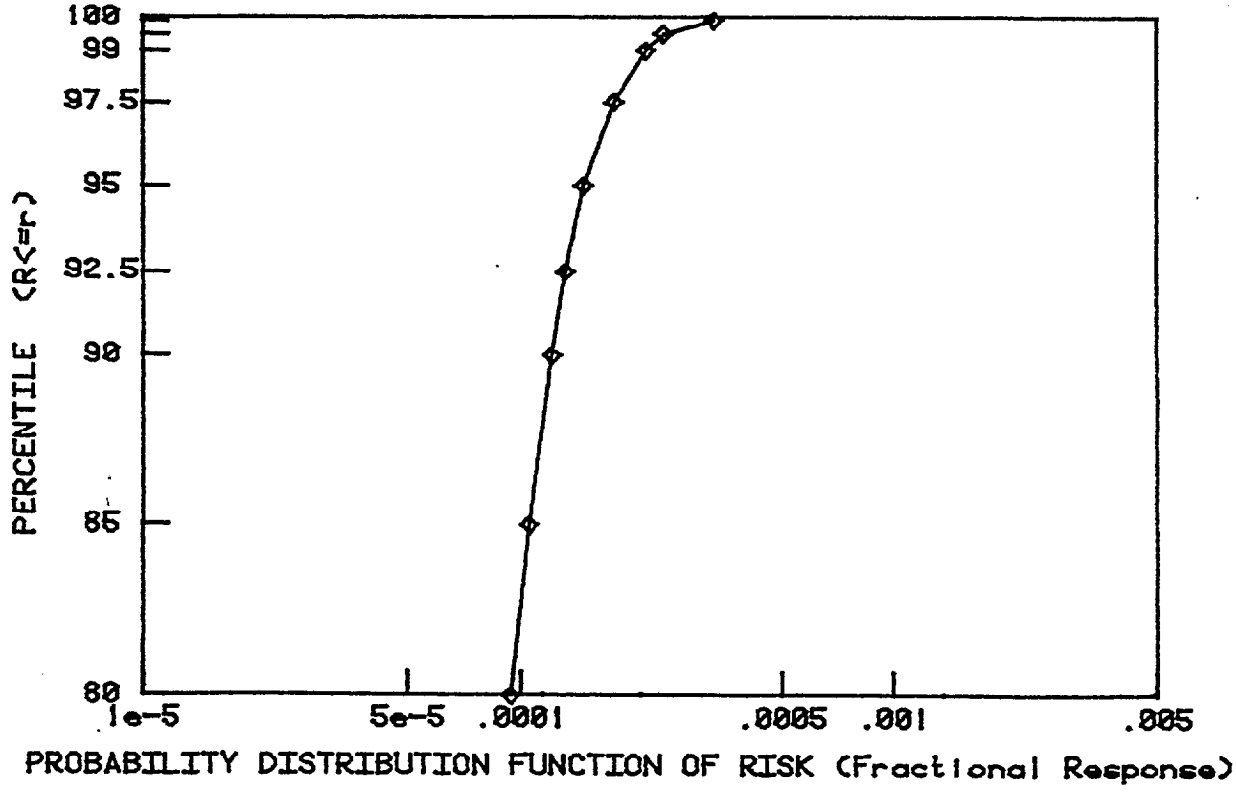
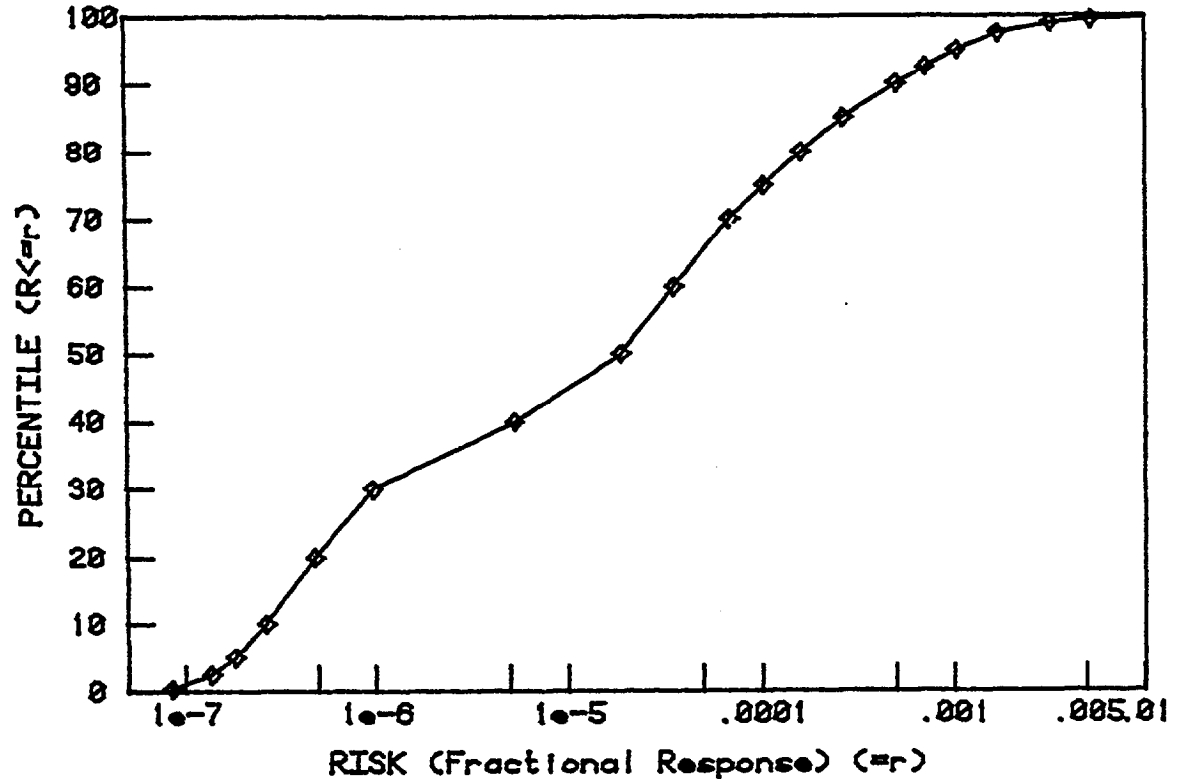



Figure 4: UNCERTAINTY IN c and P(d)



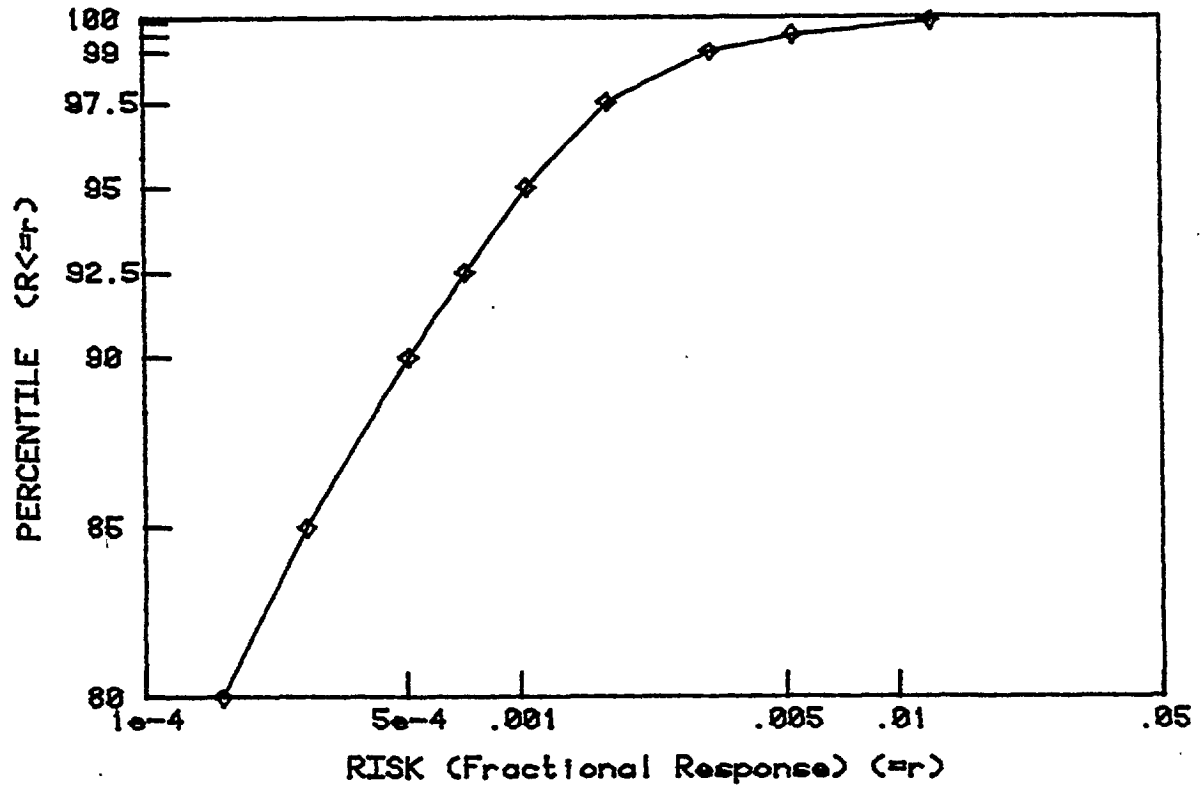
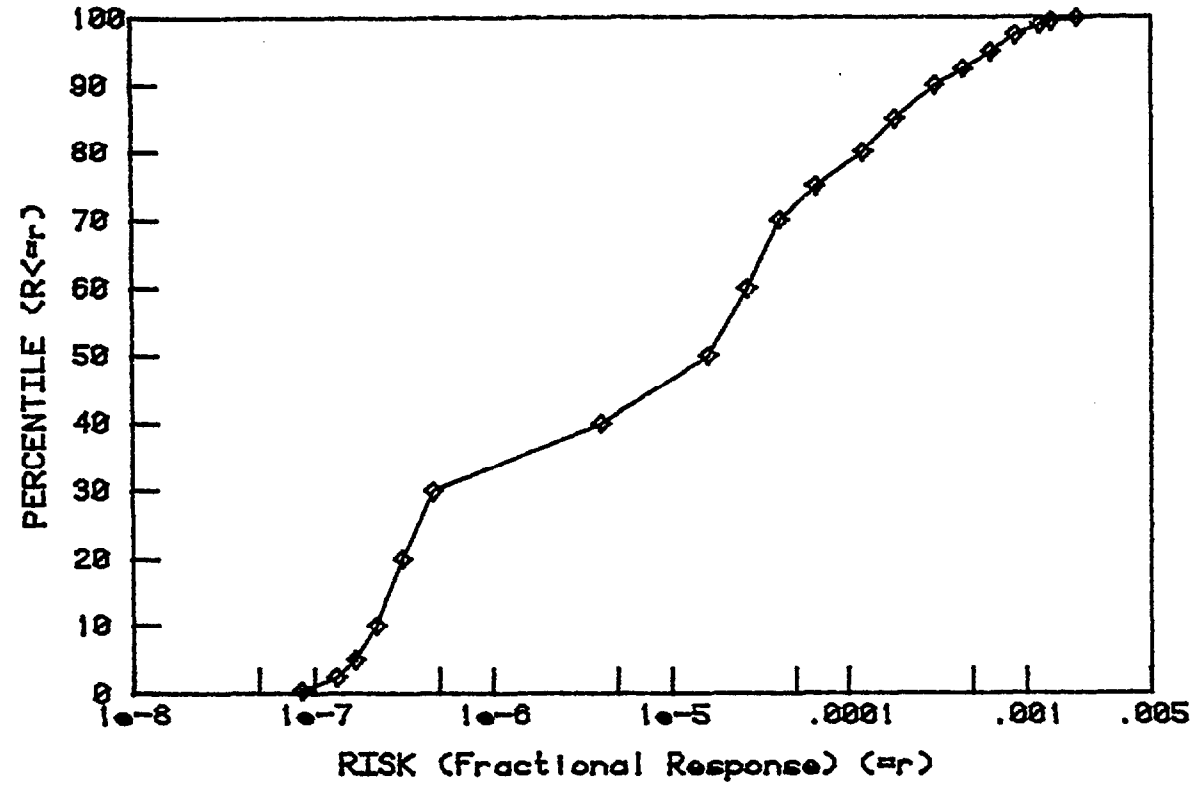



Figure 5: UNCERTAINTY IN c and a



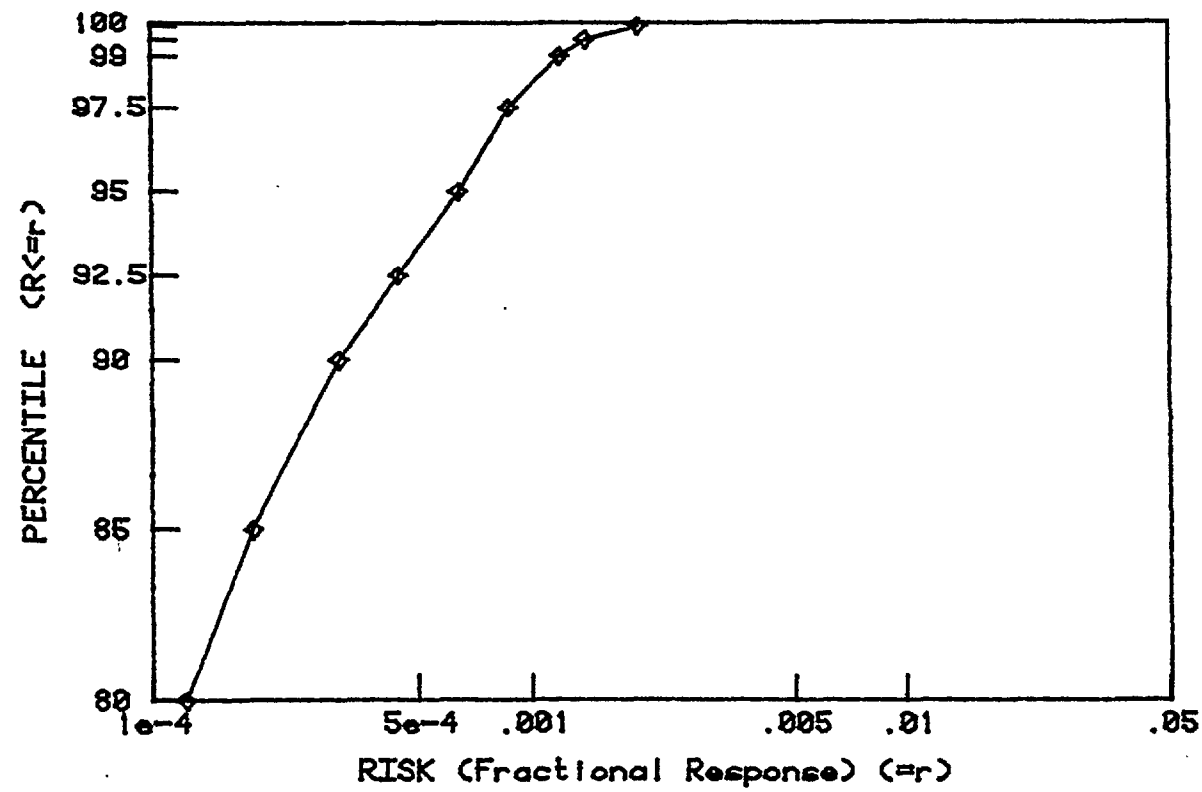
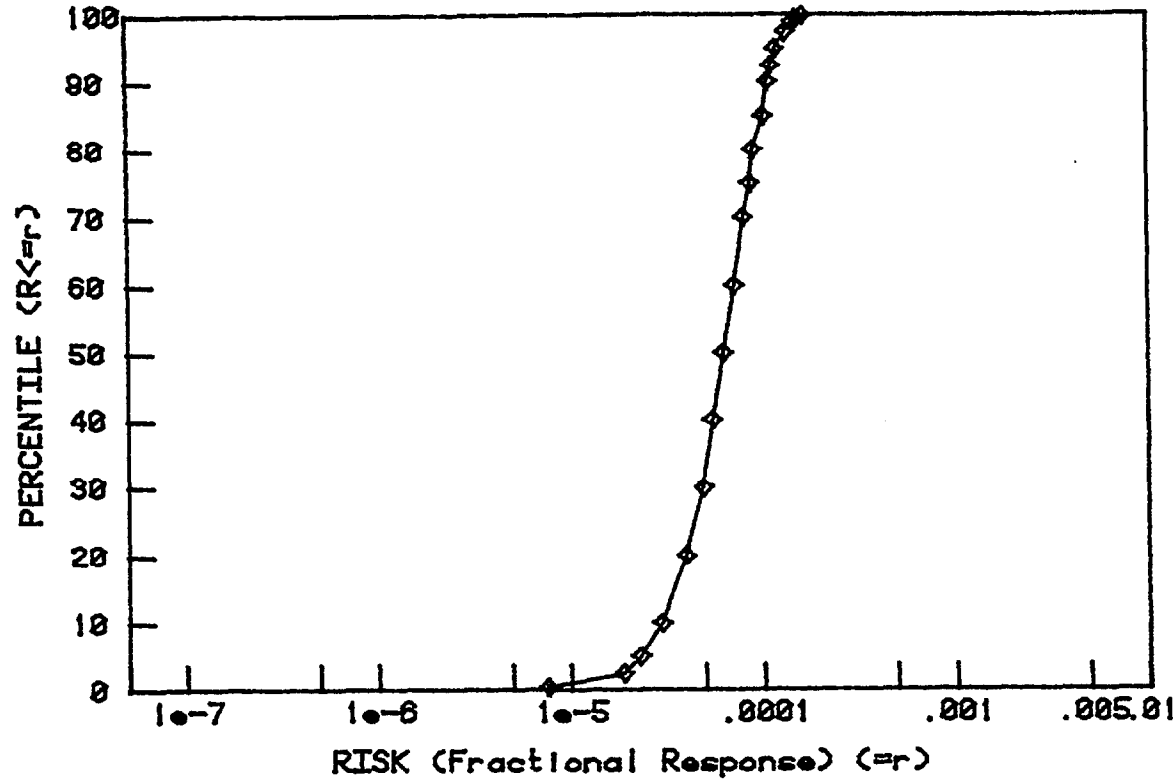



Figure 6: UNCERTAINTY IN P(d)



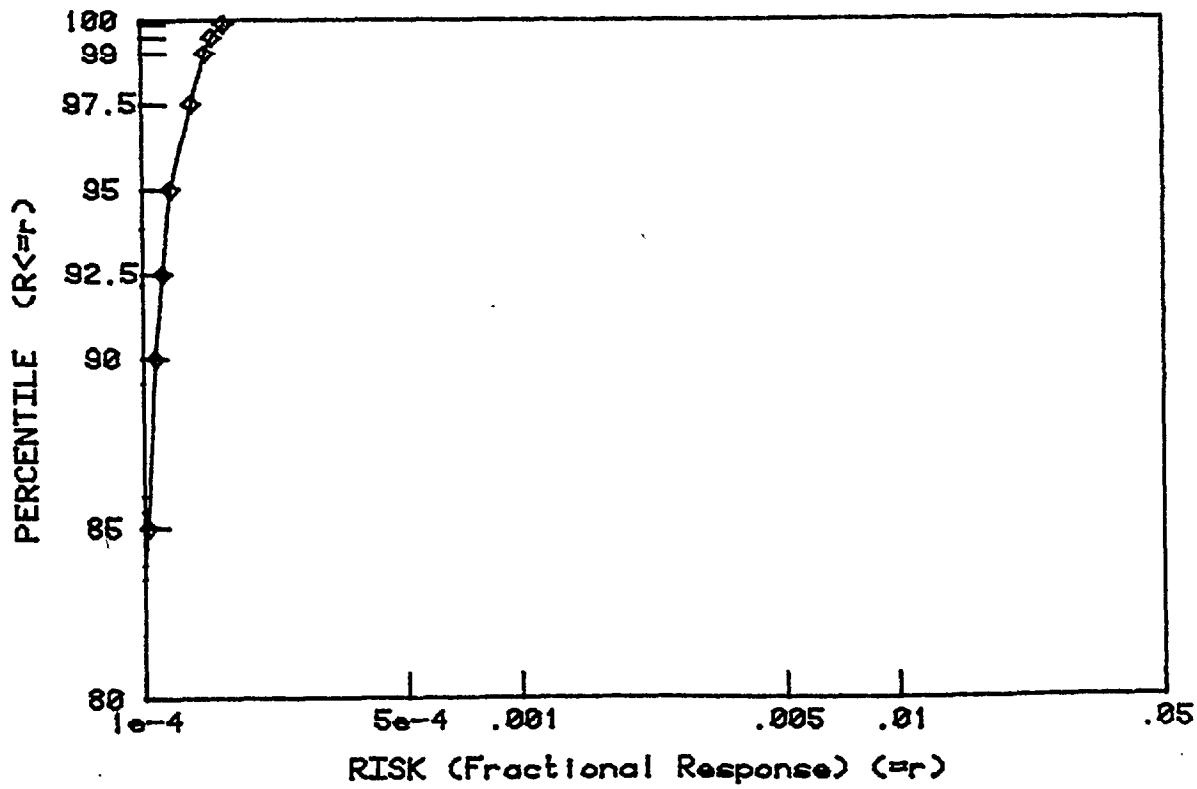
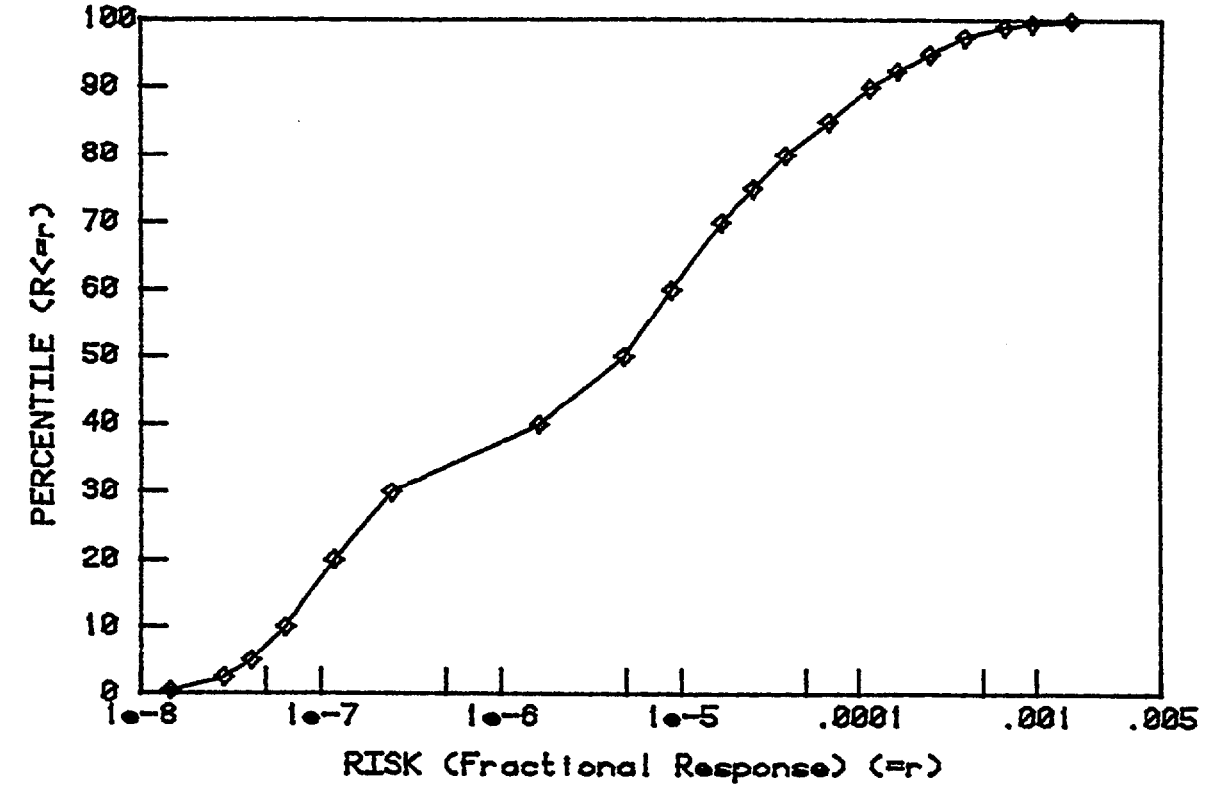



Figure 7: UNCERTAINTY IN c, a, and Q(d)



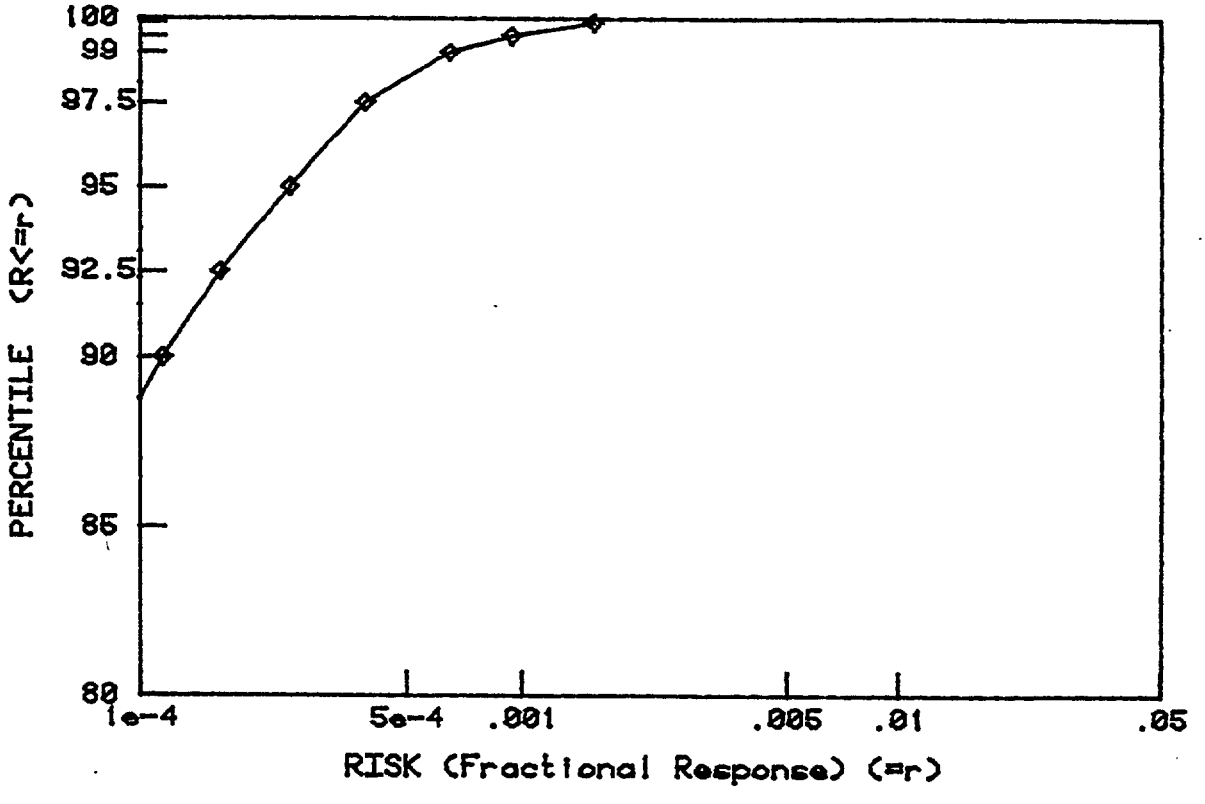
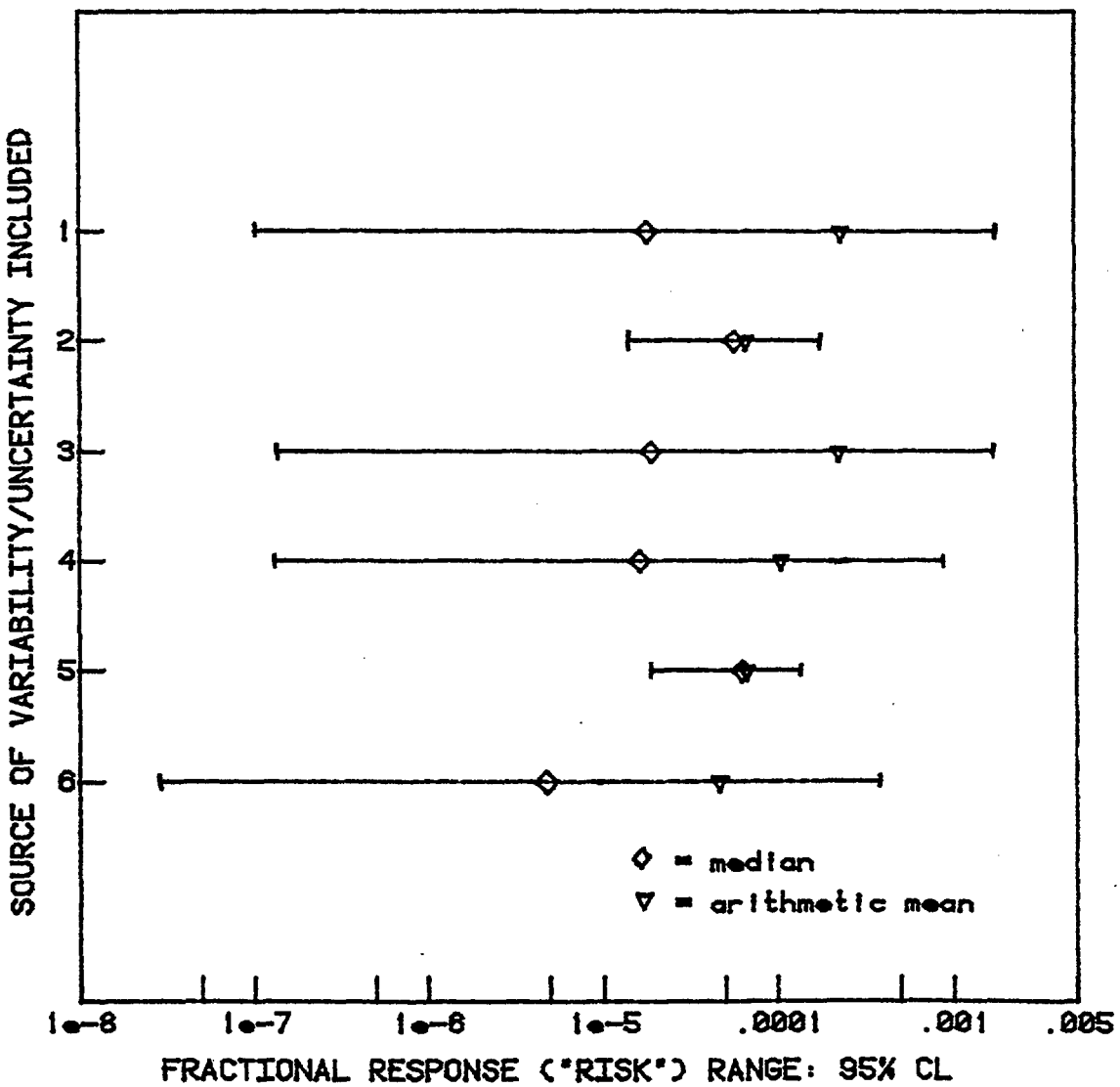



Figure 8: DBCP CANCER RISK UNCERTAINTY: COMPARATIVE ANALYSIS




| KEY: | No. | Uncertainty Source(s) |
|---|---|---|
| | 1 | c, a, P(d) |
| | 2 | a, P(d) |
| | 3 | c, P(d) |
| | 4 | a, a |
| | 5 | P(d) |
| | 6 | a, c, Q(d) |

# BIBLIOGRAPHY

Albert, R. E., R. E. Train, and E. Anderson, "Rationale developed by the Environmental Protection Agency for the assessment of carcinogenic risks," J. Natl. Cancer Inst., vol. 58, pp. 1537-1541, 1977.

Crump, K.S., H.A. Guess, and K.L. Deal, "Confidence intervals and test of hypothesis concerning dose response relations inferred from animal carcinogenicity data," Biometrics, vol. 33, pp. 437-451, 1977.

Crump, K.S., "An improved procedure for low-dose carcinogenic risk assessment from animal data," J. Envir. Pathol. Toxicol., vol. 5, no. 2, pp. 675-684, 1981.

EPA, EPA Tolerance Paper, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C., 1978.

EPA, Re-evaluation of DBCP Risks Incorporating Recent Chronic Testing Data, U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, D.C., 1979. (memo from E.L. Anderson to Jeff Kempter, Special Pesticides Review Division: 12 Jun. 1979).

EPA, "Chlorobenzilate: Position Document 3 and Domestic Animal Hazard Evaluation," (EPA/SPRD-80/35), pp. 28-30, U.S. Environmental Protection Agency, Office of Pesticide Programs, Special Pesticide Review Division, Washington, D.C., 1980a.

EPA, The Carcinogen Assessment Group's Method for Determining the Unit Risk Estimate for Air Pollutants, U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, D.C., 1980b. (8 Aug. 1980).

EPA, "Pesticide Registration Guidelines Subdivision F: Human and Domestic Animal Hazard Evaluation," (EPA-540/9-82-025), U. S. Environmental Protection Agency, Washington, D.C., 1982.

EPA, U.S. Environmental Protection Agency, "Water quality criteria documents," Federal Register, vol. 45, no. 28 Nov., p. 79350 f., 1980c.

EPA, U.S. Environmental Protection Agency, "Proposed guidelines for mutagenicity risk assessment," Federal Register, vol.

45, no. 13 Nov., pp. 74984-74988, 1980d.

Guess, H.A. and K.S. Crump, "Low-dose-rate extrapolation of data from animal carcinogenicity experiments--analysis of a new statistical technique," Mathematical Biosciences, vol. 32, pp. 15-36, 1976.

Guess, H.A., K.S. Crump, and R. Peto, "Uncertainty estimates for low-dose-rate extrapolations of animal carcinogenicity data," Cancer Research, vol. 37, pp. 3475-3483, 1977.

Guess, H.A. and K.S. Crump, "Maximum likelihood estimation of dose-response functions subject to absolutely monotonic constraints," Annals of Statistics, vol. 6, no. 1, pp. 101-111, 1978a.

Guess, H.A. and K.S. Crump, "Best-estimate low-dose extrapolation of carcinogenicity data," Envir. Health Perspectives, vol. 22, PP. 133-151, 1978b.

IRLG, Interagency Regulatory Liaison Group, "Scientific bases of identification of potential carcinogens and estimation of risks," Federal Register, vol. 44, no. (6 July), pp. 39858-39879, 1979.

Jackson, R.J., C.J. Green, J.T. Thomas, E.L. Murphy, and J. Kaldor, Literature review on the toxicological aspects of DBCP and an epidemiological comparison of patterns of DBCP drinking water contamination with mortality rates from selected cancers in Fresno County, California 1970-1979: Report to the California Dept. of Food and Agriculture by Epidemiology Studies Section, California Dept. Health Services, Berkeley, CA, 1982.

NAS, Drinking Water and Health, pp. 19-62, National Academy of Sciences, Washington, D.C., 1977.

NAS, Identifying and Estimating the Genetic Impact of Chemical Mutagens, National Academy of Sciences, Washington, D.C., 1982.

NAS, Committee on Prototype Explicit Analyses for Pesticides, Regulating Pesticides, p. 66f., National Academy of Sciences, Washington, D.C., 1980.

Shell Oil Company, Risk Assessment for DBCP; interoffice memorandum from C.S. Smith to C.E. Stehr; submitted as comments on EPA Proposed Rulemaking for drinking water (48 FR 45502, 5 Oct. 1983), Houston, TX, 1983.