Application of Probabilistic Methods to Noncarcinogenic Risk Assessment: A Case Study of Hexachloroethane and Paraquat

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ABSTRACT

Examples are developed as to how a probabilistic representation of the uncertainty in the Reference Dose (RfD) can be applied in a comparative risk analysis for a hypothetical population exposed to two compounds - hexachloroethane and paraquat. The primary noncancer risk assessment tool in the current USEPA Risk Assessment Guidance for Superfund is the hazard quotient (HQ), in which the estimated exposure dose is divided by the RfD. The risk analysis tools used in the examples are the HQ and a model for estimating risk above the RfD (Price et al., 1997). The approach utilizes a distributional characterization of the uncertainty factors (UFs) and of the exposures. The examples are presented with both the default ("reference") UF distributions and empirical UF distributions. Distributions of dose rates used in this assessment were chosen so that the point-estimate hazard quotient for the high-end exposed individual is the same for each compound. The two chemicals, however, differ in total RfD uncertainty and in the steepness of their dose-response curves. The RfD for paraquat includes two areas of uncertainty while the hexachloroethane RfD has three. Experimental data show a 50% response in test animals at twice the NOAEL for paraquat and at 10 times the NOAEL for hexachloroethane, indicating a steeper slope for paraquat. The probabilistic analysis estimates that the 95th percentile HQ for the high end exposure to paraquat is 2 times higher than for hexachloroethane when the reference UF distributions are used, but equivalent to hexachloroethane when the empirical distributions are used. The analysis further indicates that the relative population risk at the 95th percentiles (for both exposure and RfD uncertainty) for paraquat is more than 10-fold greater than for hexachloroethane using the reference UF distributions, while it is only 2-fold greater using the empirical distributions. This analysis demonstrates that the use of empirical distributions can significantly affect risk management decisions. Thus, the pursuit of additional data with which to define empirical distributions is an important effort.

INTRODUCTION

The USEPA has established RfDs for hexachloroethane and paraquat based on studies in laboratory animals (IRIS, 1996). The RfD for hexachloroethane is based on a subchronic rat study (Gorzinski et al., 1985) in which an NOAEL of 1 mg/kg-day was established. Uncertainty factors of 10 each were applied in the derivation of the RfD to account for interspecies extrapolation uncertainty, interindividual variability, and for extrapolation from a subchronic to a chronic toxicological endpoint. The resulting RfD was calculated as 0.001 mg/kg-day. The RfD for paraquat is based on a chronic dog study (Chevron Chemical Company, 1983) which identified a NOAEL of 0.45 mg/kg-day. Two uncertainty factors of 10 each were applied to the NOAEL to account for interspecies extrapolation and interindividual variability, resulting in an RfD of 0.0045 mg/kg-day.

The purpose of this analysis was to explore the impact of the uncertainty in the RfDs on hazard estimates involving the two compounds. Hazard was characterized using both the traditional hazard quotient methodology (USEPA, 1989) and the dose-response methodology proposed by Price et al. (1997). Both the reference uncertainty distribution (Swartout et al., 1997a) and empirical distributions (Gillis et al, 1997; Schmidt et al., 1997; Swartout et al., 1997b) were used in the analyses to investigate the effect of preliminary information on distributions derived from empirical data.

DESCRIPTION OF ANALYSES

Four risk characterization analyses were conducted. Each analysis was conducted twice; first with the reference distribution (Swartout et al., 1997a) and then with empirical uncertainty distributions (Gillis et al., 1997; Schmidt et al., 1997; Swartout et al., 1997b). First, the uncertainty in the hazard quotient for the high-end exposed individual, defined as the individual at or above the 90th percentile exposure, was calculated using a dose corresponding to the 95th percentile of the distribution of doses in a population and the uncertainty distribution for the sensitive population NOAEL (Carlson-Lynch et al., 1997). The distributional RfD was calculated by dividing the NOAEL in animals by the product of the relevant uncertainty distributions.

Second, distributions of hazard quotients representing population variability in exposures were estimated as the ratios of the uncertainty distributions for an individual's exposure and the distributional RfDs. Upper and lower 90% confidence intervals on the distributions were calculated using the dose distribution and the 5th and 95th percentile RfDs from the distributional RfD.

Third, the uncertainty in the response rate for the high end exposed individual was calculated using the dose-response model presented by Price et al. (1997). Fourth, the response rates in the population were calculated, and upper and lower 90% confidence intervals on the response rates were estimated using the 5th and 95th percentile dose-response relationships.

A description of the input data is presented in Table 1.

Table 1. Inputs for Hexachloroethane and Paraquat Reference Dose and Dose-Response Calculations

Variable	Input	Reference
Chemical-Specific Inputs		
Hexachloroethane		
Critical Endpoint	atrophy and regeneration of renal tubules	Gorzinski et al., 1985
NOAELa	1 mg/kg-day	Gorzinski et al., 1985
ED50a	8.63 mg/kg-day	MLE from benchmark dose model
Species	rat	
Uncertainty Factors	UFh, UFa, UFs	USEPA, 1997
Modifying Factors	none	USEPA, 1997
Reference Dose	0.001 mg/kg-day	USEPA, 1997
Dose Distribution	lognormal (base e), μ = -5.8, s = 0.75 (mg/kg-day)	Assumed
95^{th} Percentile Dose (HEE)	0.01 mg/kg-day	Assumed
Paraquat		
Critical Endpoint	chronic pneumonitis	Chevron Chemical Company, 1983
NOAELa	0.45 mg/kg-day	Chevron Chemical Company, 1983
ED50a	1.1 mg/kg-day	MLE from benchmark dose model
Species	dog	
Uncertainty Factors	UFh, UFa	USEPA, 1997
Modifying Factors	none	USEPA, 1997
Reference Dose	0.0045 mg/kg-day	USEPA, 1997
Dose Distribution	lognormal(base e), μ = -4.3, s = 0.75	Assumed
95^{th} Percentile Dose (HEE)	0.045 mg/kg-day	Assumed
Uncertainty Distributions		
Reference Uncertainty Distribution	lognormal (base 10), μ = 0.3349, s = 0.3765	Swartout et al., 1997a
Empirical Uncertainty Distributions		
UFh	empirical distribution of effective dose ratios	Gillis et al., 1997
UFa-rat	empirical distribution of dog/man MTD ratios	Schmidt et al., 1997
UFa-dog	empirical distribution of rat/man MTD ratios	Schmidt et al., 1997
UFs	lognormal (base e), μ = 0.7743, s = 1.152	Swartout et al., 1997b

NOAELa = Animal No-Observed-Adverse-Effect-Level
$ED_{50}a$ = Animal Effective $Dose_{50}$
MLE = Maximum Likelihood Estimate
UFh = Interindividual Uncertainty Factor
UFa = Interspecies Uncertainty Factor
UFs = Subchronic to Chronic Extrapolation Uncertainty Factor
HEE = High End Exposure (USEPA, 1992)

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RESULTS

Figures 1 and 2 show the probability distributions for the sensitive human population NOAELs (NOAELh) resulting from the reference and empirical distributions, respectively, compared with the current RfD for each chemical. Figures 3 and 4 compare the HQ uncertainty distributions for hexachloroethane and paraquat that result from the reference and empirical UF distributions, respectively. Using the reference distributions, paraquat is shown to exhibit approximately a 2-fold greater hazard quotient at the 95th percentile than hexachloroethane. The HQs for both compounds at the 97.5th percentile are less than the point estimate HQ of 10. Using the empirical distributions, the HQ uncertainty distributions appear comparable for the two compounds, and the 97.5th percentile for each compound exceeds the point estimate value of 10.

Population distributions of hazard quotients (incorporating exposure variability) for hexachloroethane and paraquat, with 90% confidence intervals, are shown in Figures 5 and 6 for the reference and empirical distributions, respectively. Figure 5 shows that the upper confidence interval distribution for paraquat reaches a hazard quotient of 1 at about the 30th percentile, while upper confidence interval distribution for hexachloroethane does not reach 1 until the 67th percentile. By contrast, the use of the empirical distributions indicates that the upper confidence interval distributions for both compounds reach 1 between the 10th and the 20th percentiles (Figure 6). Neither the reference nor empirical distributions show hazard quotients reaching 10 at the upper 90% confidence interval on the 95th percentile.

Figures 7 and 8 show uncertainty in the response rate for doses 10 times higher than the RfD. Again, using the reference distributions (Figure 7), greater hazard is predicted for paraquat (the 95th percentile response exceeds 10%) than for hexachloroethane (the 95th percentile response is less than 2%). The empirical distributions suggest more similar responses (Figure 8; 10% for paraquat and 5% for hexachloroethane at the 95th percentile).

Finally, Figures 9 and 10 show the upper 90% confidence intervals on population response rates above the RfD. Use of the reference distributions indicates that the 95th percentile response for paraquat is more than 10-fold greater than the 95th percentile response for hexachloroethane; use of the empirical distributions indicates that the difference is only about 2-fold. Median response distributions for both chemicals and both uncertainty distribution types were zero through the 95th percentiles except for paraquat using the reference distributions, where the dose received by the 95th percentile of the population was estimated to be associated with 1% response.

Figure 1. Uncertainty in Reference Dose Using the Reference UF Distribution

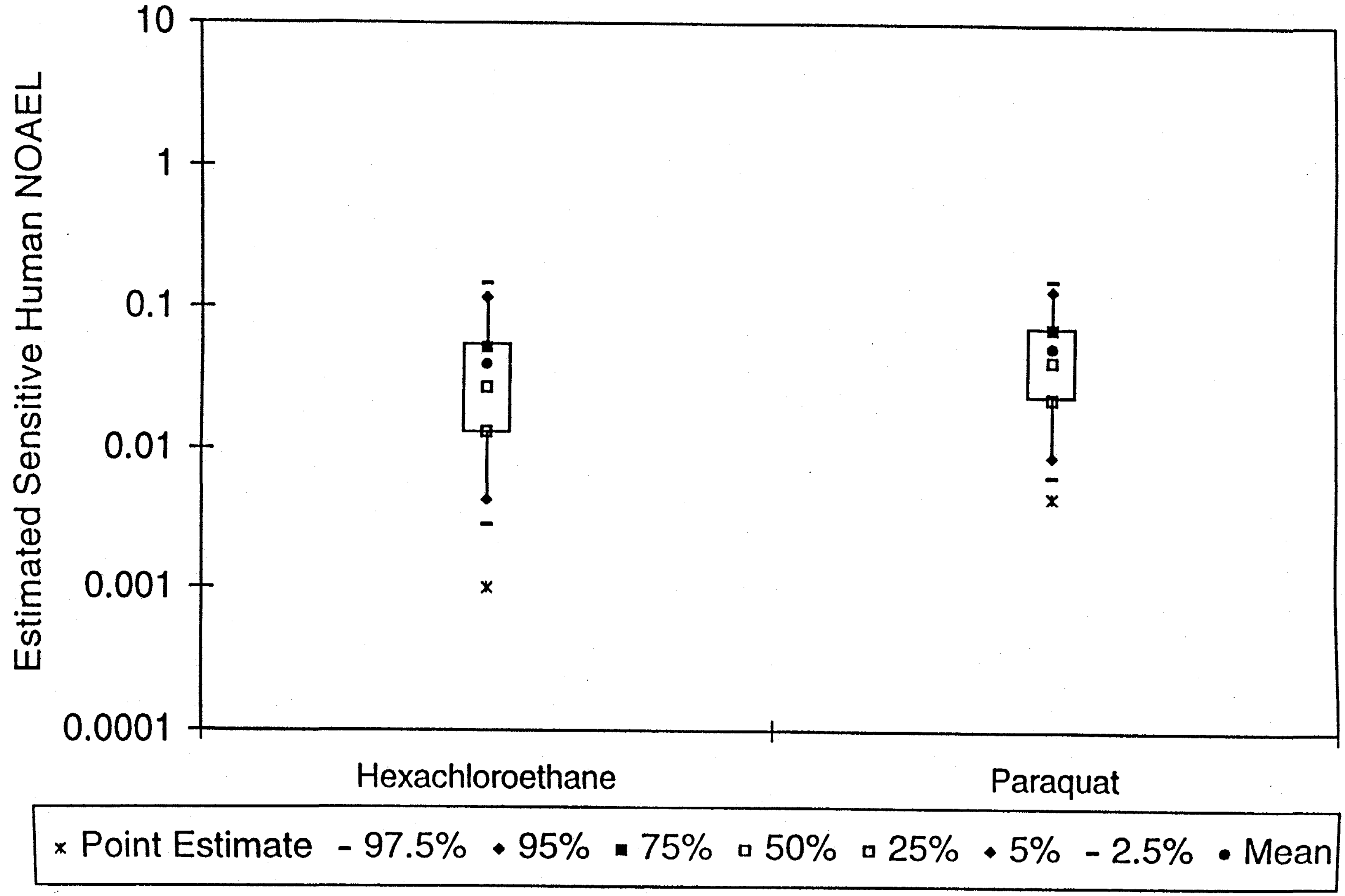

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Figure 2. Uncertainty in Reference Dose Using the Empirical UF Distributions

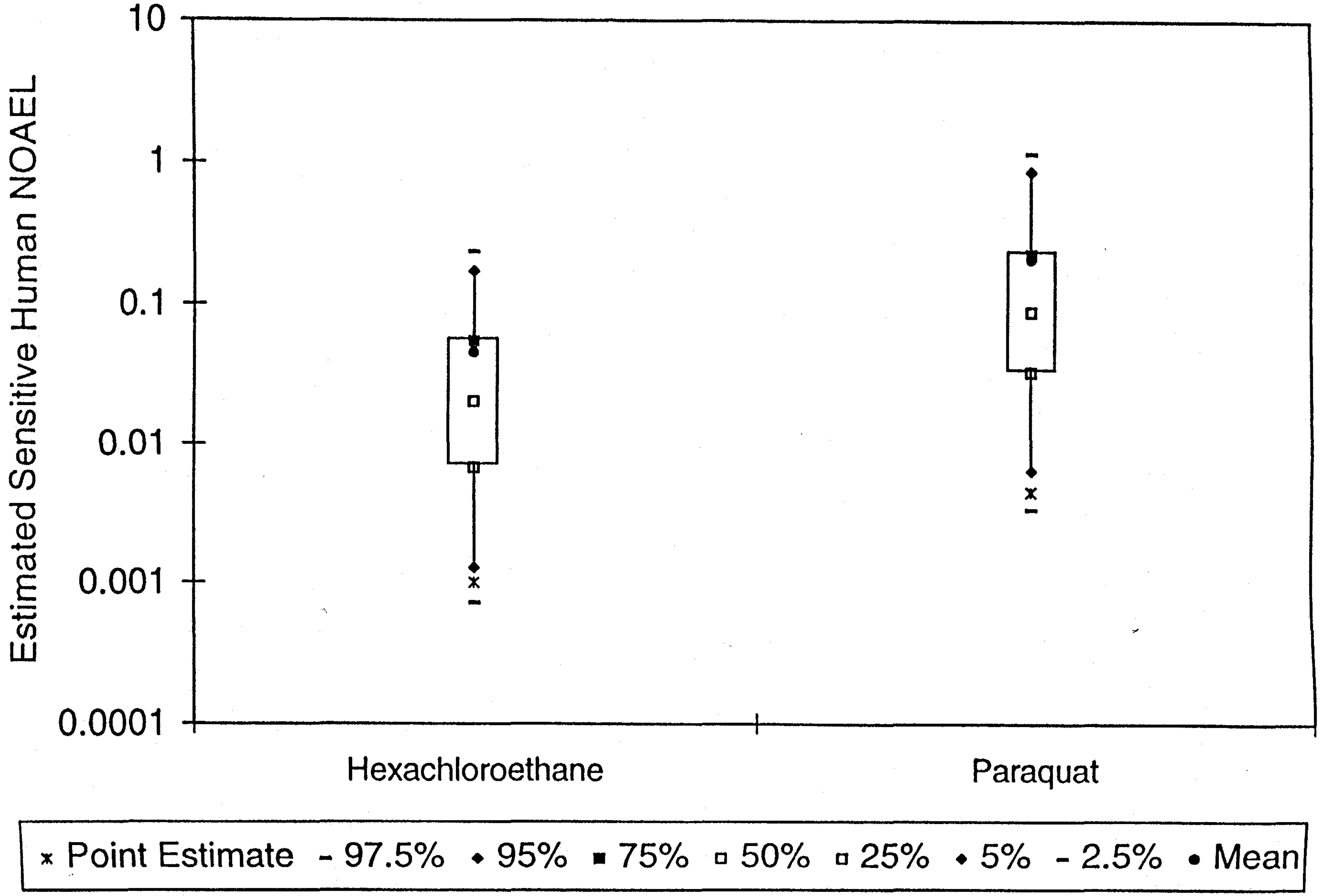

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Figure 3. Uncertainty in Hazard Quotients Using the Reference UF Distribution

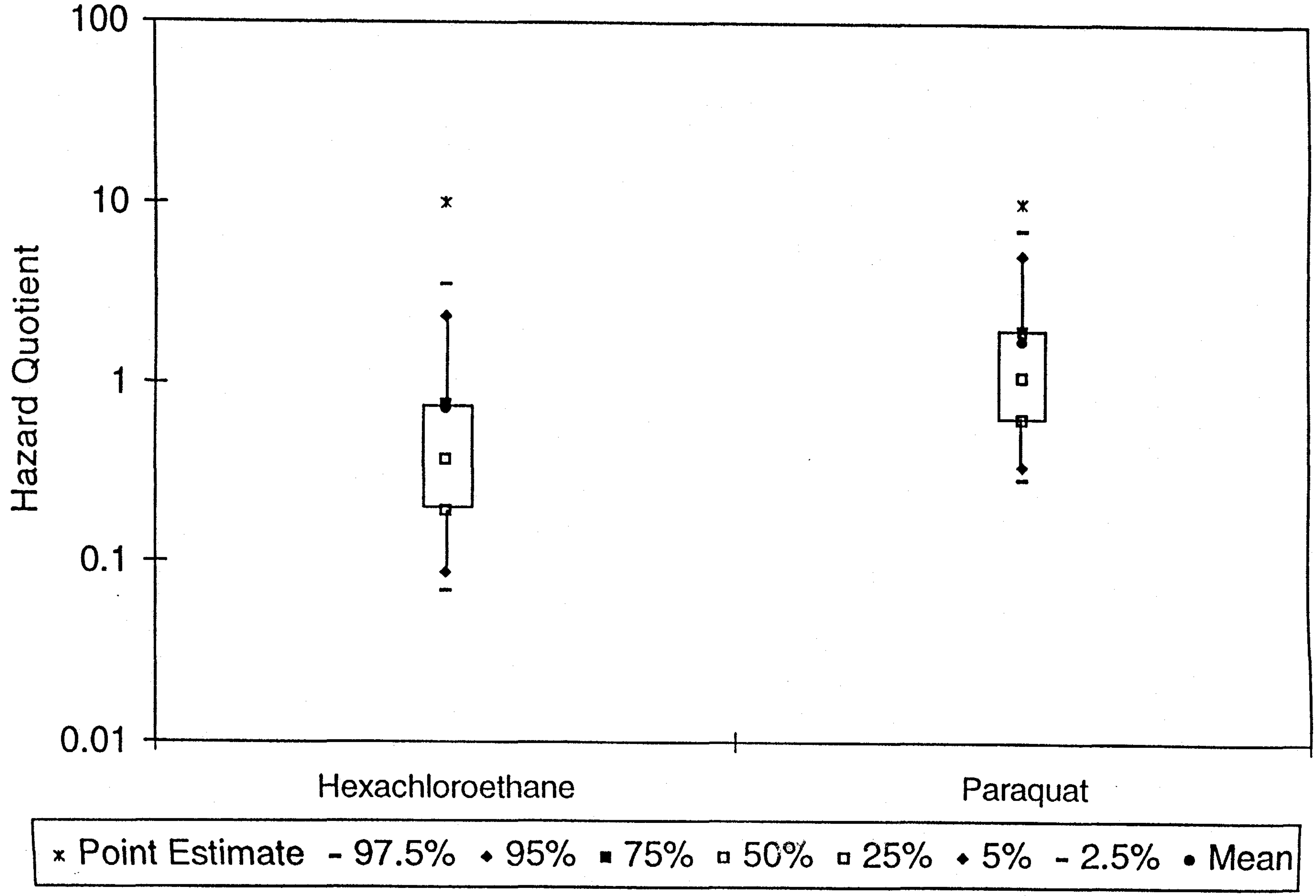

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Figure 4. Uncertainty in Hazard Quotients Using the Empirical UF Distributions

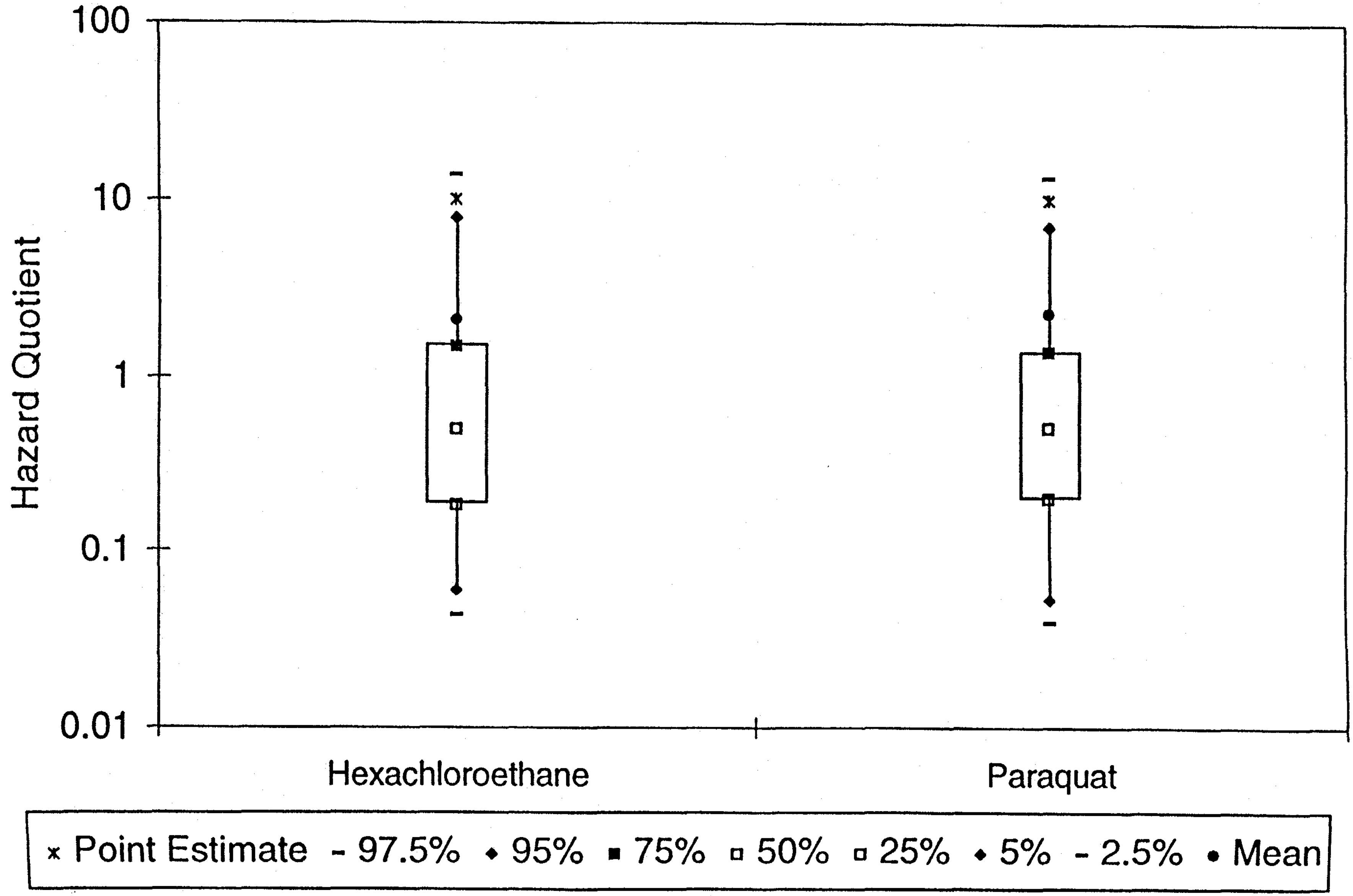

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Figure 5. Population Hazard Quotients with 90% Confidence Intervals Using Reference UF Distribution

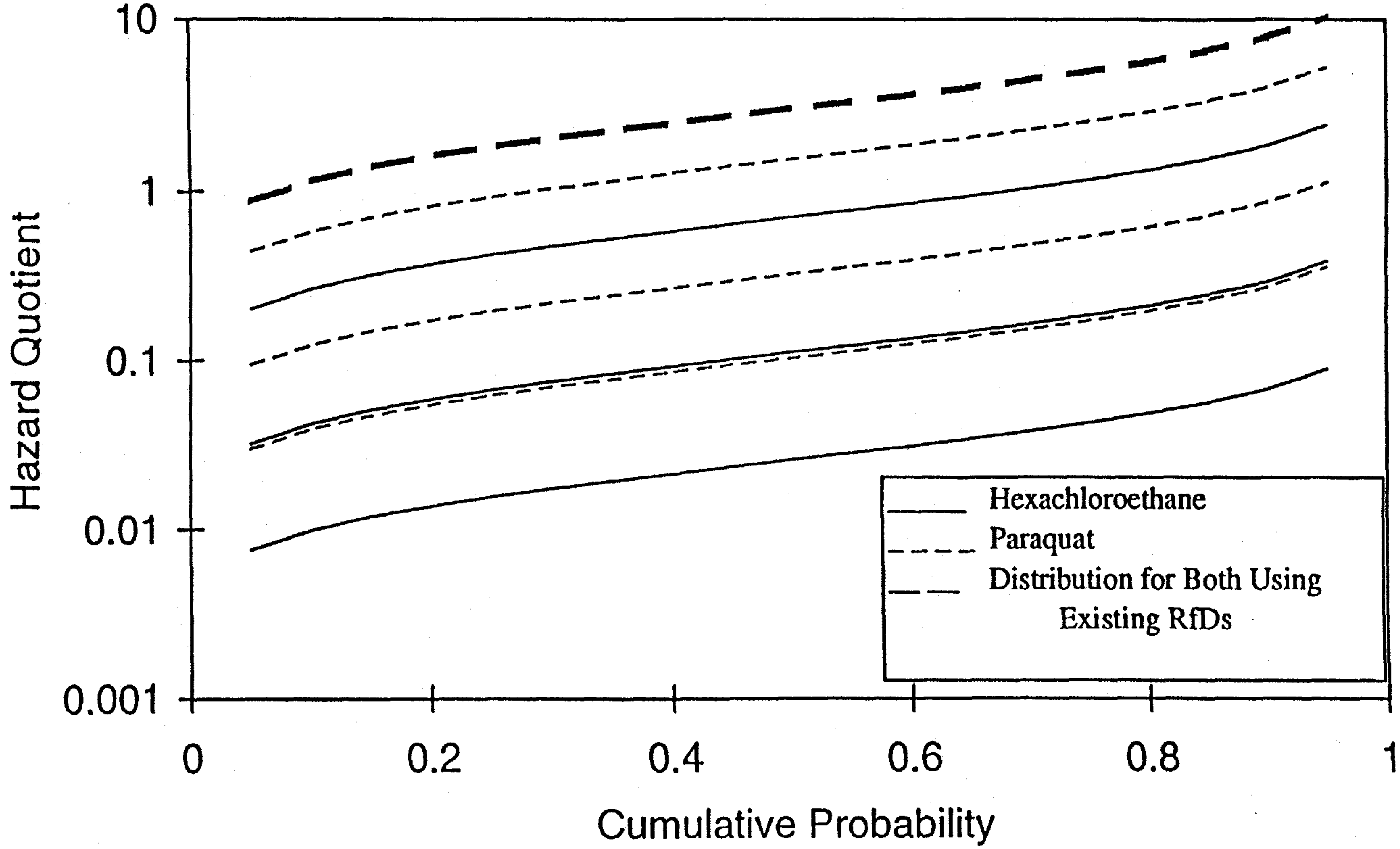

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Figure 6. Population Hazard Quotients with 90% Confidence Intervals Using the Empirical UF Distributions

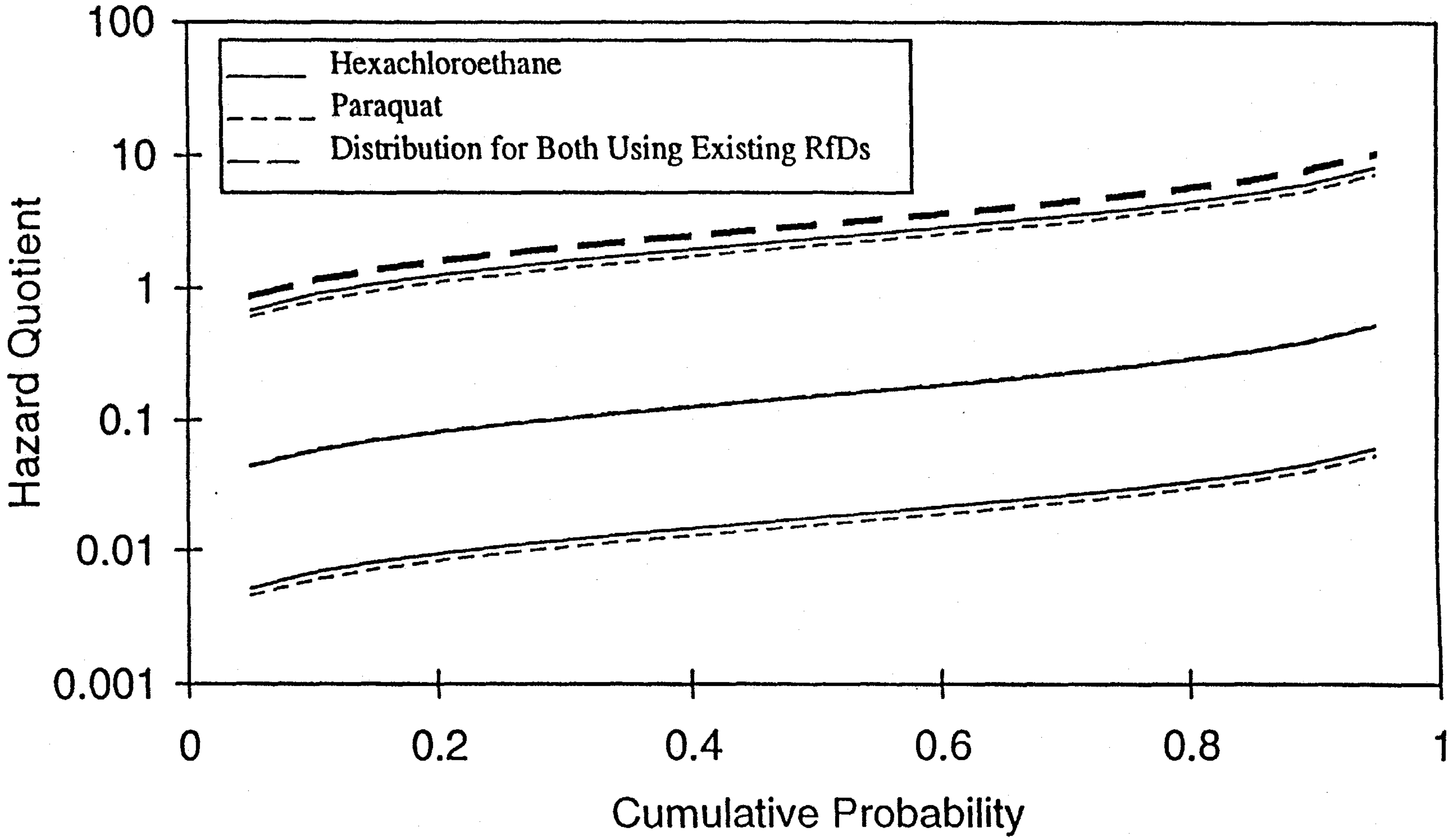

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Figure 7. Uncertainty in Response at the High End Exposure Using the Reference UF Distribution

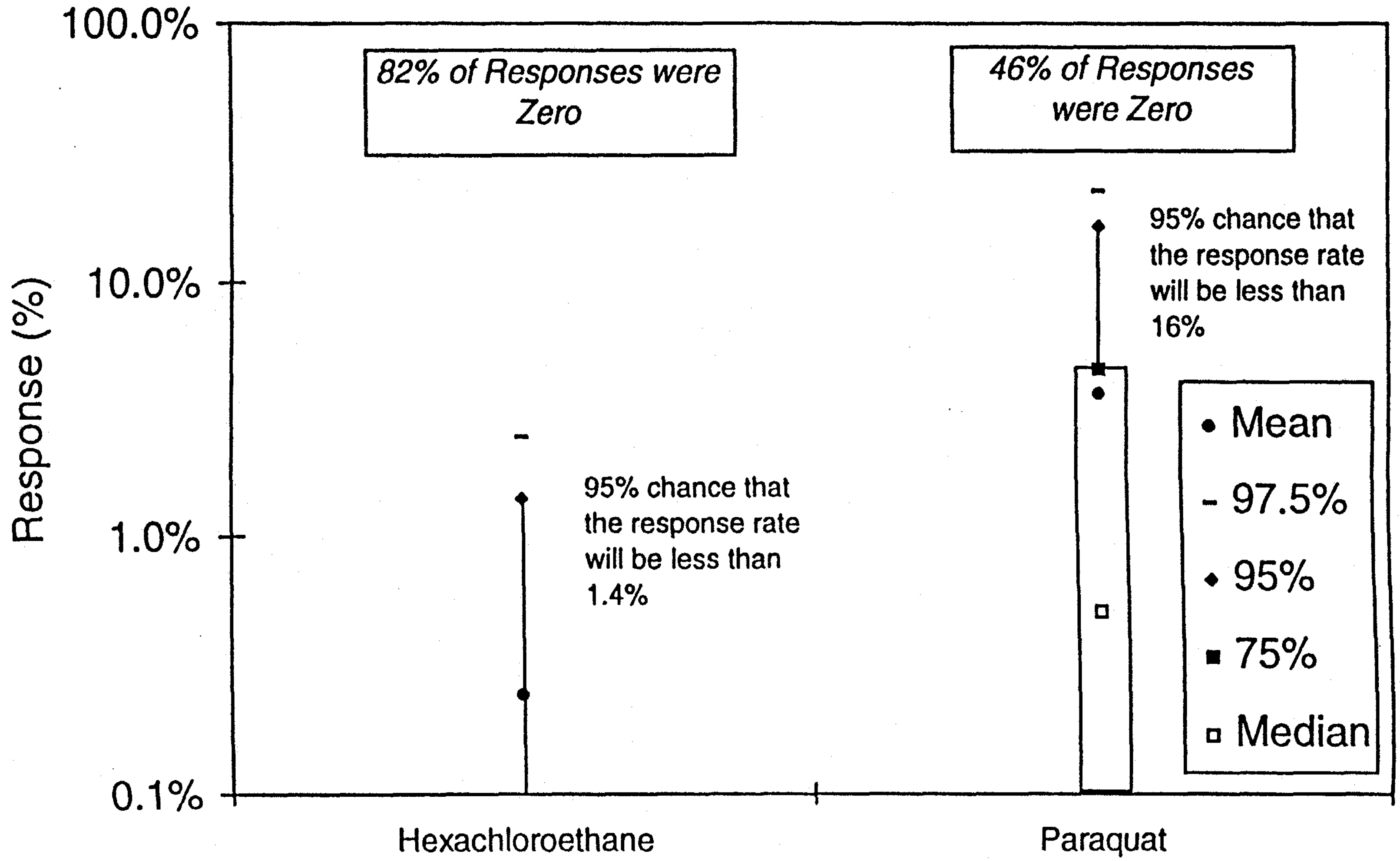

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Figure 8. Uncertainty in Response at the High End Exposure Using the Empirical UF Distributions

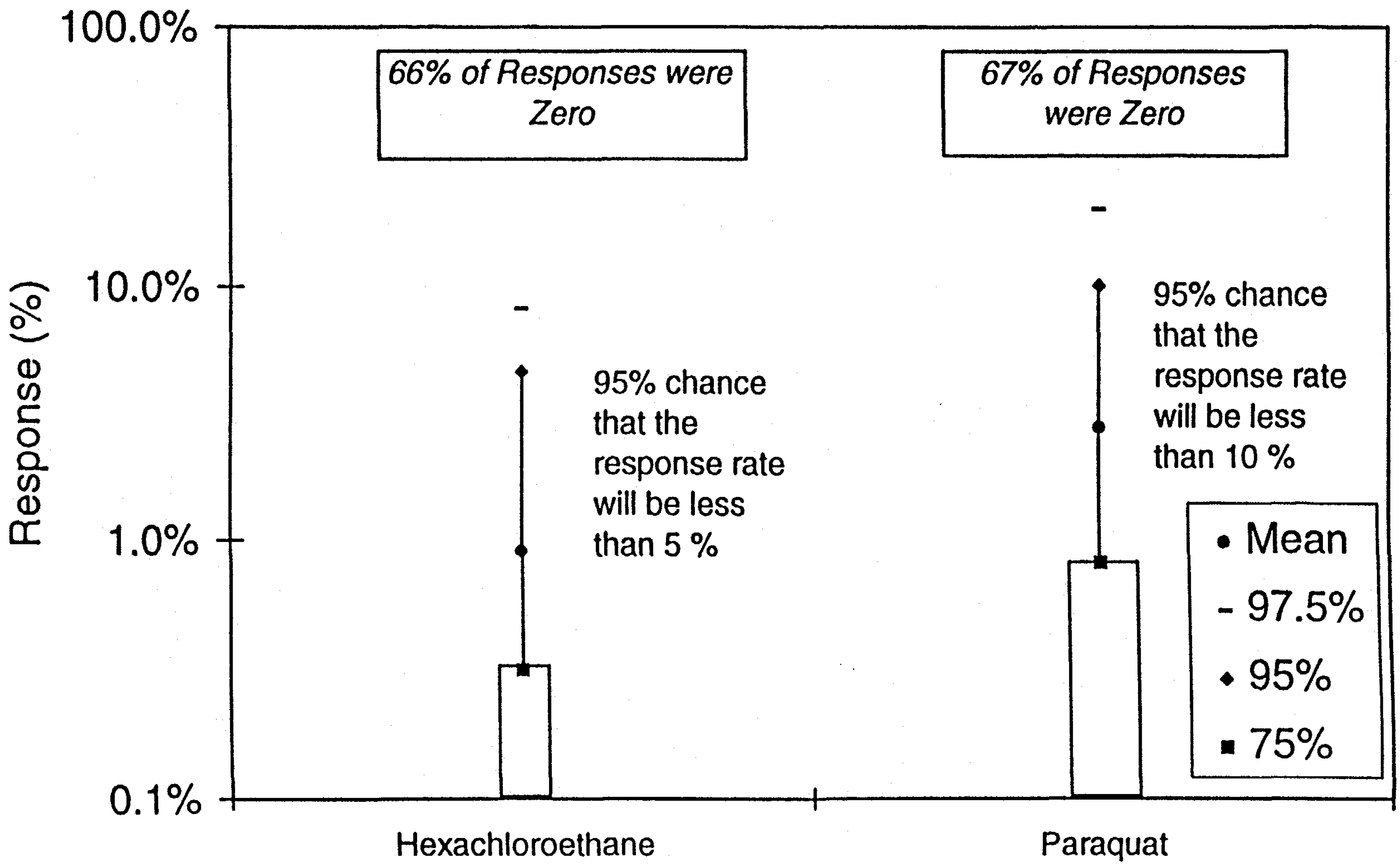

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Figure 9. Population Response Based on Noncancer Dose-Response Model Using the Reference UF Distribution

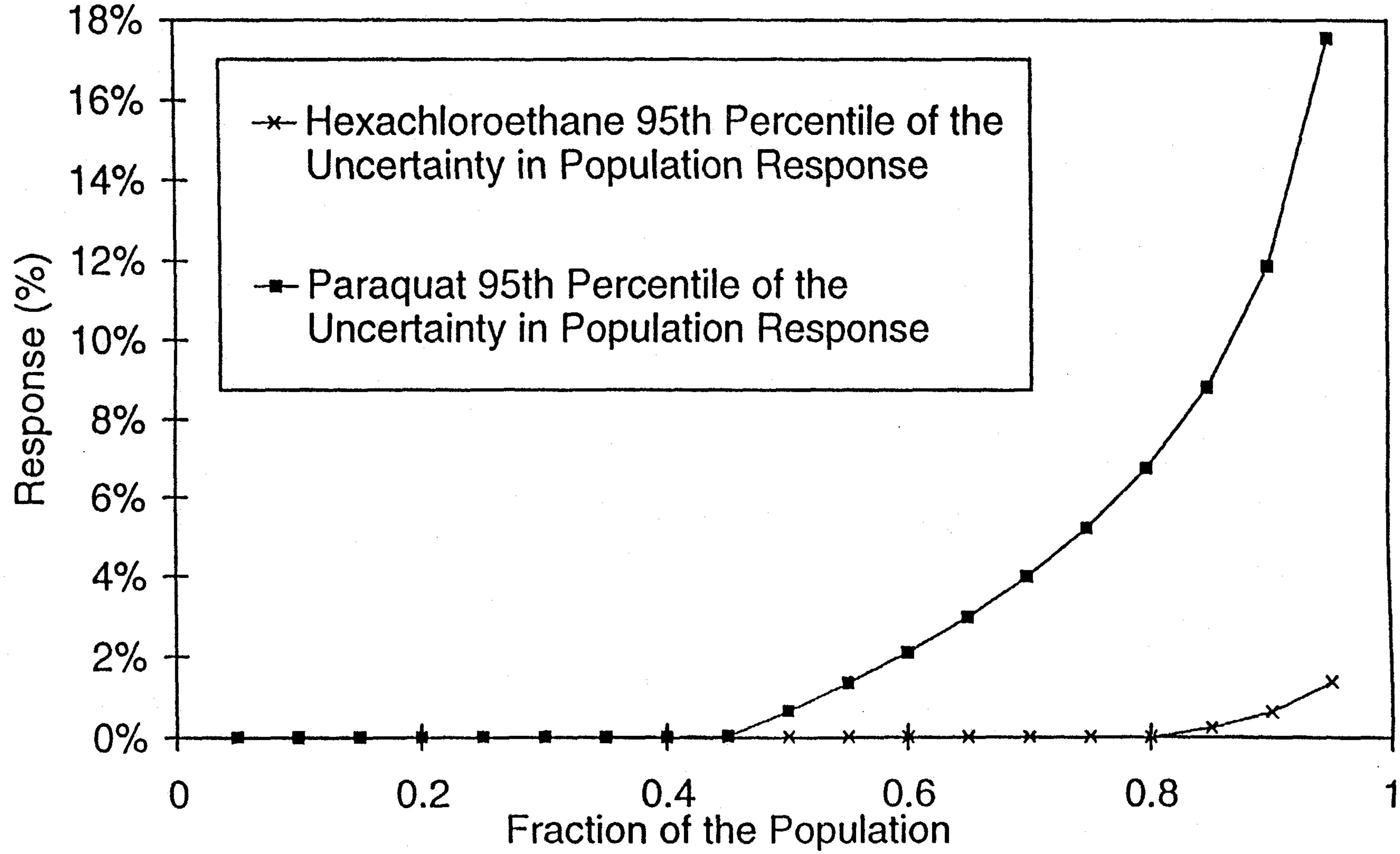

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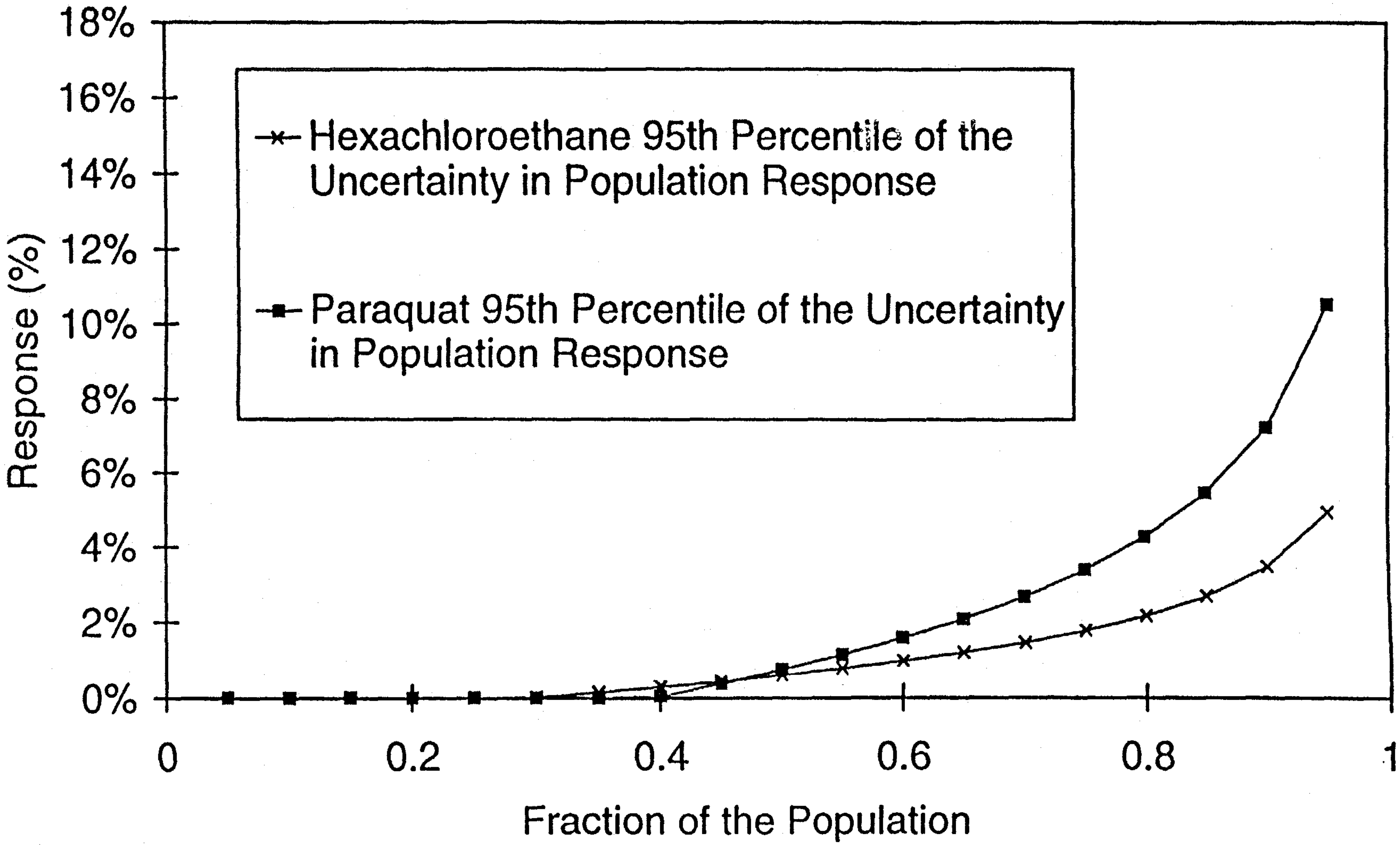
Figure 10. Population Response Based on Noncancer Dose-Response Model Using the Empirical UF Distributions



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CONCLUSIONS

- A probabilistic-based approach to RfD uncertainty conveys more information to risk managers on noncancer risk measures than does current guidance.

- Nominally equivalent hazard quotients can differ significantly with a probabilistic assessment of RfD uncertainty.

- Empirically-derived UF distributions can result in qualitatively different conclusions than those based on default UF distributions.

- Relative risks for doses above the RfD are much higher for paraquat than for hexachloroethane using the reference UF distribution, but are virtually the same using the empirical UF distributions.

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Studies on the human health effects and risks associated with exposure to PCBs, including from fish consumption, show:

- Neurobehavioral and developmental problems--such as impaired responsiveness, short-term memory problems, and reduced mental abilities in the infants and children of mothers exposed to PCBs prior to and during pregnancy (Jacobson, 1984, 1985, 1990; Koopman, 1996; Huisman, 1995; Lonkey, 1996; Rogan, 1985); and
- Three times the chance of having lower IQ scores; twice the chance of lagging at least two years behind in reading comprehension; short-term and long-term memory effects and difficulties in paying attention (Jacobson, 1996); and
- Increased risk of cancer and immune system effects among the general population, and workers producing PCB capacitors (Bertazzi, 1987; Brown, 1987; Sinks, 1991; Svensson, 1984; Rothman, 1997).

Because of the potential health impacts, fish consumption advisories for both the Lower Fox and Green Bay have been in place since 1976. However, not all people follow fish advisories. These advisories, published regularly by the Wisconsin Department of Natural Resources (WDNR), warn residents to limit or eliminate locally-caught fish (e.g. carp, catfish) from their diet. They also provide tips on how to properly clean and cook fish to reduce the risk of PCB exposure.

OTHER PCB SEDIMENT CLEANUPS

Since the 1980's, EPA and local government agencies have addressed PCB contamination at many other rivers and harbors. Often, these cleanups have included dredging as part of the solution. Suction or hydraulic dredging has been shown to remove sediments very safely. Other cleanup options include leaving less contaminated sediments in place and capping of PCB hot spots. Dredging has been highly effective in removing PCBs and, when measured, has shown to greatly reduce contaminants in fish and wildlife at sites including Sheboygan (WI), Ruck Pond (WI), Manistique Harbor (MI), Shiawassee River (MI), Waukegan Harbor (IL), and the St. Lawrence River (NY).

For the Lower Fox, preliminary evaluations suggest that dredging may be part of any comprehensive cleanup, although no decision has been made at this time. If dredging is selected, a number of factors would have to first be considered, including the amount of material to be dredged and the levels of contamination.

PCBs can also have a tremendous impact on natural resources. In studies conducted since the 1970's, fish and wildlife populations throughout the Great Lakes have shown high levels of PCB build up in fatty tissues, resulting in reduced fertility, deformities (e.g. cross bills in cormorants), physiological abnormalities, and death. Currently, the Lower Fox and Green Bay have levels of PCBs in water, fish, and other wildlife which range from about 100 to 10,000 times safe levels. Without action on the PCB contaminated sediments, it may take 100 years or more for PCB in the Lower Fox and Green Bay to reach acceptable levels.

When PCBs and other contaminants are allowed to remain in a major water body like the Lower Fox, there may be economic impacts, as well. Contaminated water resources are known to limit local economic potential and revenue resulting from tourism, sport fishing, commercial fishing, and waterfront development. Conversely, where rivers and harbors have been cleaned, local economic conditions have been enhanced. The build up of contaminated sediments in the river has made it difficult for the Army Corps of Engineers to keep the Lower Fox shipping channel open, affecting commerce.

What can be done about PCBs in the Lower Fox River?

A group of six governmental agencies and tribal entities is working together to move forward with cleanup of the Lower Fox. Under the Federal Superfund toxic cleanup program (administered by EPA), responsibility for much of the cleanup work lies with a group of paper mills known as the Fox River Group. The six partners: EPA, WDNR, U.S. Fish and Wildlife Service (FWS), National Oceanic and Atmospheric Administration (NOAA) and the Menominee and Oneida Tribes. Other agencies supporting the effort include: Wisconsin Department of Public Health and Family Services, and the Agency for Toxic Substances and Disease Registry.

Actual cleanup must be preceded by a comprehensive risk assessment, analysis of cleanup alternatives, and/or environmental engineering design work. A range of cleanup strategies may be considered, and will include many opportunities for public comment and input from the other affected parties.

For More Information

If you have additional questions about PCBs, health studies, or the Lower Fox River cleanup, please contact: Bri Bill, EPA Community Involvement Coordinator, 1-800-621-8431 x36646 or (312) 353-6646.