7. INTERPRETATIONS TAKEN FROM THE CASE STUDY

7.1. WHAT THE CASE STUDY DOES AND DOES NOT ACCOMPLISH

The current case study provides an example of how the CRFM detailed in Chapter 4 can simultaneously assess the cost effectiveness of different drinking water treatment options based on their impacts on several disparate health conditions, including sensitive subpopulations. It is intended to further develop the CRFM, identify important health risk factors, recognize data gaps, and choose directions for investigations of other treatment options. The case study is not intended to provide definitive answers; rather, the discussions in this chapter are intended to illustrate the type of inferences that can be drawn from a CEA analysis, while acknowledging that changes to the specific assumptions used in the case study could conceivably change the findings of Chapter 6.

The CRFM approaches the problem of evaluating alternative drinking water disinfection technologies by augmenting the NAS risk assessment paradigm (NAS, 1983) with methods drawn from the fields of health economics and decision sciences. These approaches are established and well-accepted in other areas of public health and have direct applicability within the field of risk management. Nonetheless, they are not typically used in the area of environmental risk analysis. Moreover, the assessment of alternative drinking water disinfection technologies draws on a wide range of scientific disciplines including chemistry, decision sciences, drinking water treatment engineering, epidemiology, pathogenic microbiology, infectious disease microbiology, probability and statistics, and toxicology. The dependence of the CRFM on so many different areas of expertise complicates a complete understanding of this tool. For these reasons, the assumptions

and calculations used when applying the CRFM must be clearly laid out so that experts from various disciplines can understand them and relate them to their own fields of study. This clarity of presentation would also be helpful to other individuals and groups that make decisions concerning the treatment of public waters or that want to apply the CRFM to other public health or environmental interventions.

The CRFM, unlike most traditional risk assessments, is constructed as a predictive model rather than as a protective one. The CEA uses central tendency values rather than high-end, conservative, "protective" values, that are useful in many other risk management contexts, so that alternative strategies can be evaluated without inappropriately placing more weight on one set of risks (by, for example, overstating their likelihood) as compared to others. Distributions are used in place of point estimates for parameters with substantial uncertainty so that the analysis can quantify the cost-effectiveness (CE) ratio's uncertainty and identify those parameters for which improved precision would most strengthen confidence in the results. In addition, for any simulation procedure, the input parameters must be estimated using comparable values. The simulation results would be meaningless if, for example, 95% upper bound point estimates are used for one parameter while another parameter is estimated using a central tendency estimate and assuming a normal distribution. The CRFM fully describes the analysis results, including best estimates, a scientific evaluation of the extremes, a discussion of the limitations, and an analysis of uncertainty; thus the amount of information that is provided for the end user is optimal.

The simulation procedure performed in the present case study accounts for the variability and uncertainty that is described by the parameter distributions. Figures 6-3 and 6-4 show the cumulative distributions of 1000 CE ratios for the general population and the AIDS population,

respectively. For each of 1000 calculations, the computer program sampled from the input distribution for each parameter and then computed the CE ratio. This procedure generated a distribution of 1000 CE ratios that represent the possible outcomes for the CE ratios, given the input parameter distributions. Figures 6-3 and 6-4 can be interpreted as the probability (Y-axis) that the CE ratios are less than or equal to a given dollar/QALY value (X-axis). The simulation does not, however, account for any uncertainties that are not represented by the input distributions. For example, because the case study was performed for a hypothetical, single treatment plant, the results cannot be generalized to represent results for all similar plants at a regional or a national level because the distributions of certain parameters such as the DBP concentrations or *Cryptosporidium* source water concentrations are likely to be different and to have more variability.

One of the major limitations found in developing the case study is that there remain key areas where very little or no data exist. Specifically, additional data and improved analytical methods are needed to better quantify source water *Cryptosporidium* oocyst concentrations and treatment efficacy. Additional research efforts are needed to measure the infectivity and exposure-dependent morbidity/mortality of *Cryptosporidium*. This analysis could be greatly improved by the development of a sensitive and reliable method for detecting and quantifying infectious *Cryptosporidium* oocysts in drinking water. Additionally, a better understanding of the factors affecting the distribution of interindividual susceptibility to waterborne *Cryptosporidium* in both the general population and the immunocompromised population is critical; these data could lead to the identification of additional susceptible subpopulations. These data gaps limit the confidence that can be placed in the results of the analysis.

In the current case study, DBP risks turn out to be of far less importance than the microbial risks. However, for another set of treatment trains and source water conditions, this may not be the case. Several factors contribute to the uncertainty of risks associated with DBPs. For instance, stochastic uncertainty in bioassay data yields a range of plausible cancer slope factors, an issue addressed in section 5.3 by developing lognormal distributions for this parameter using the MLE and upper bound estimates. Further sources of uncertainty in the predictions of risk arise from exposure-related factors such as the concentrations of DBPs in drinking water and variations in patterns of drinking water intake. Varying degrees of confidence in the extrapolation of animal-derived toxicity values to humans, the presence of sometimes large amounts of unidentified halo-organic materials, and the assumption of response-addition as the basis for summing risks across the mixtures components all add to the uncertainty for this risk.

The present case study is also considered a demonstration, and not a definitive assessment, because it does not address all of the important issues surrounding this problem. Specific areas that still must be addressed include:

- The impact of treatment system failures, events that are highly unlikely but which may result in severe consequences related to microbial risk.
- The evaluation of secondary (person-to-person) transmission of microbial disease, as occurs during any epidemic, irrespective of source.
- Investigations into variations or gradations of treatment options, such as variations in disinfectant contact time, gradations of disinfection concentrations, and differences in residual concentration.
- Effects of drinking water distribution systems, including time spent in the distribution system prior to consumption, on the concentrations of disinfectants, DBPs, and waterborne pathogens to which individuals are actually exposed.
- Inclusion of other pathogens (e.g. *Giardia*) that, under certain conditions, are also responsible for waterborne outbreaks.

- Evaluation of chemical risks not associated specifically with disinfection, but that may be affected by disinfection processes; for example, the risks from contaminants such as heavy metals and pesticides are assumed to be constant across the treatment options evaluated, but may not be.

- Quantification of the financial impact of health effects, including factors such as the costs associated with the medical treatment of disease states, the costs associated with morbidity-related reductions in the workforce, financial costs associated with long-term health care, etc.

- Investigations of effects on other sensitive subpopulations, such as infants or the elderly. The AIDS population in the case study was intended to be a surrogate for the immunocompromised in order to show how to include a sensitive subpopulation in the analysis.

7.2. INTERPRETATIONS OF THE RESULTS

For this case study, EPA generated central tendency estimates, distributions or ranges for the model parameters from data that vary widely in quality and certainty (see Chapter 5). Predictive models, expert judgment, or assumptions were used and so noted when empirical data were unavailable, and the associated uncertainty was characterized. As is true for any simulation procedure, the quality and certainty of the input parameters directly influence the validity of the results. In this case study, it is clear from the sensitivity analyses (see Tables 6-15, 6-16, and 6-18) that most of the uncertainty stems from the lack of data available to accurately estimate parameters related to *Cryptosporidium*: concentrations of infectious oocysts in the source water, removal efficacy of the treatments, infectivity rates, and conditional probabilities related to contracting mild illness, contracting moderate to severe illness, or dying. Figure 7-1 illustrates that this is an extremely important point because microbial morbidity and mortality drive the results of the case study, while the risks associated with health endpoints related to DBP exposure are essentially inconsequential. For the in-home filter option, no change from baseline is assumed

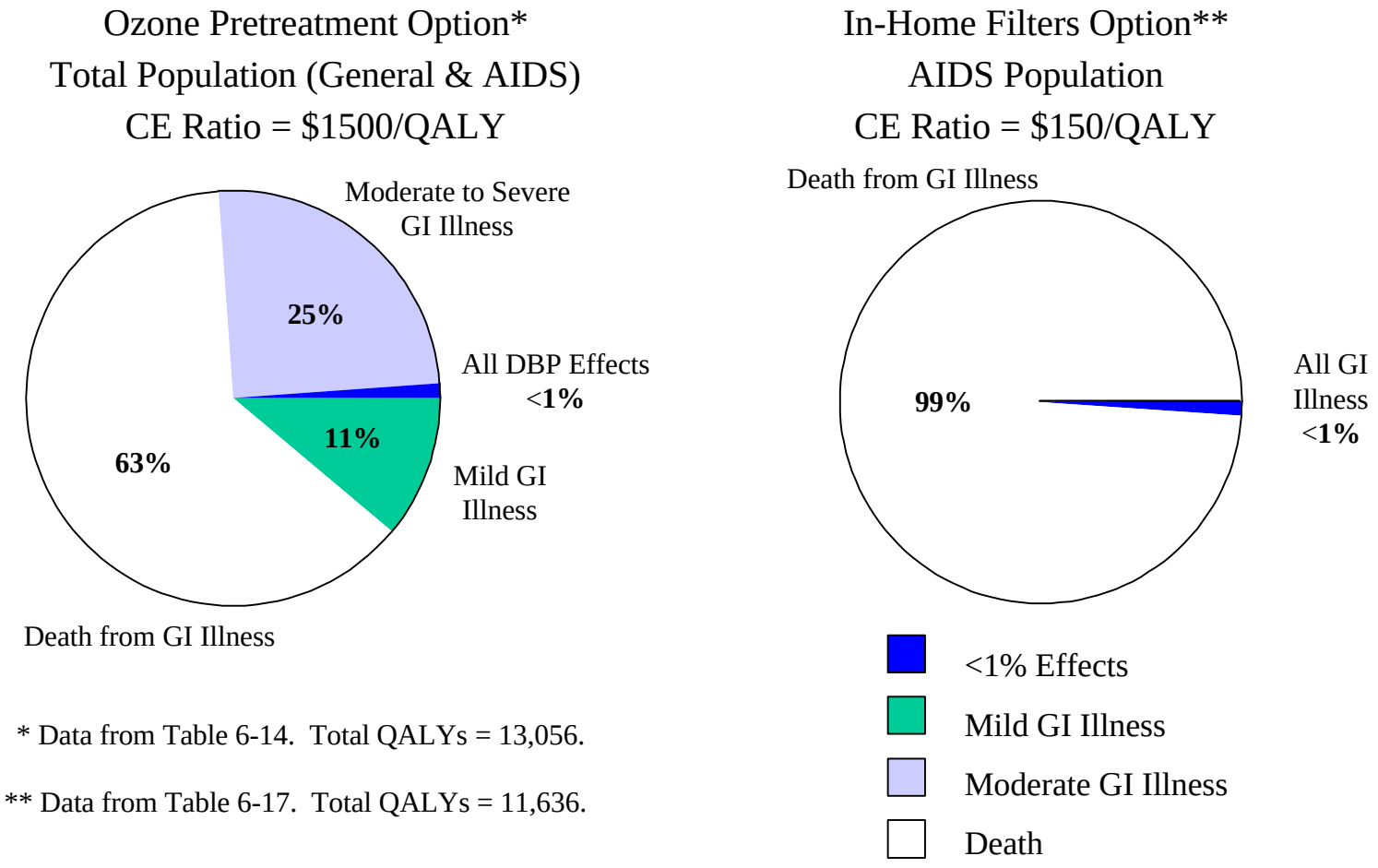
for DBP exposure, so the contribution of QALY costs for DBP-induced illness or death is zero. For the ozone pretreatment system, the QALY costs for DBP risks would have to increase by approximately three orders of magnitude in order to affect the results (see Table 6-14).

Figure 7-1 not only shows the differences between the impacts of microbial and DBP risks, but also divides the microbial risks into relative contributions of morbidity and mortality. In both of the treatment options, death from microbial illness contributes the majority of the risk as measured in lost QALYs. In the ozone pretreatment, however, mild and moderate to severe GI illness makes up 36% of the risk. For the in-home filter option, death from microbial illness overwhelms all other effects including the GI morbidity, which is less than 1%. The most important contributing factor in the analysis is the *risk of death given moderate to severe illness* that, for the AIDS population, is relatively large (approximately 5%) as compared to the general population (approximately 0.005%). Because of this difference in risks, the total lost QALYs for the AIDS population of 429 persons under the home filters option is nearly the same as those for the total population of 460,000 individuals under the ozone pretreatment option.

The case study characterizes risks associated with *Cryptosporidium* and DBP exposure by quantifying the risk of health effects, translating these to a health condition and estimating the number of discrete health events (e.g., numbers of cases of cancer, mild gastrointestinal illness, etc.), and converting them to a common metric (QALY) useful in combining and comparing their

FIGURE 7-1

Average Change from Baseline in QALYs By Health Effects



* Data from Table 6-14. Total QALYs = 13,056.

** Data from Table 6-17. Total QALYs = 11,636.

impacts. By estimating the financial costs (dollars) for each treatment option, cost-effectiveness (CE) ratios (dollars/QALY) can be calculated, and these ratios can be compared across options. It may be noted that there is no *a priori* way to determine whether an option is acceptable based on the CE ratio alone; rather, the acceptability of the CE ratio depends on what society is willing to pay per QALY, which may depend on a number of issues, such as the voluntary nature of the risks, etc. However, certain quantitative guidelines do exist, as suggested by Kaplan and Bush (1982) and shown in Table 7-1.

7.2.1. Results: Baseline Treatment Vs. Baseline Plus Ozone Pre-Treatment. For the comparison of the baseline treatment option and the ozone pretreatment supplement, both the number of health events and the amount of lost QALYs show that microbial-mediated illness and death overwhelm the health effects associated with DBP chemicals (Table 6-14). The positive change in total lost QALYs from baseline to the ozone pretreatment is an indication that the ozone pretreatment option may be a favorable choice, but the costs associated with the technology have not yet been factored in. It may also be noted that there is a small negative change in QALYs for the cancer endpoints, suggesting a slight increase in the small DBP-induced risks with the ozone pretreatment option. However, the QALY costs for mortality from microbial illness for either treatment train far exceed the QALY cost for cancer-related deaths, estimated for both the general population and the AIDS population (see Tables 6-12 and 6-13). Based on the average (i.e., expected) difference between the QALY costs for the baseline technology and the ozone pretreatment technology (bottom panel of Table 6-14), the following was noted for the total population:

TABLE 7-1

Cost Evaluations per QALY Unit[a]

Cost per QALY Ratio	Cost Evaluation
<$35,000	“cost effective by current standards”
$35,000 to $160,000	"possibly controversial, but justifiable by many current examples"
> $160,000	"questionable in comparison with other health care expenditures"

[a] Adapted from Kaplan and Bush, 1982.
[b] Costs have been adjusted to reflect the change in value of the dollar from 1982 to 1998; original cut-offs were $20,000 and $100,000 per QALY.

- The ozone technology *decreased* microbial-associated mild illness, moderate to severe illness and death QALY costs by approximately 69%.
- The ozone technology *increased* DBP-related cancer illness and death QALY costs by approximately 14%.
- The ozone technology *decreased* QALY costs for reproductive toxicity and developmental toxicity by approximately 23% and 16%, respectively.

The impact of ozone pretreatment on microbial risk reflects the increased efficacy of *Cryptosporidium* inactivation; future evaluations may be improved by assessing the health effects of additional microbes and the efficacy of both treatment options on their removal or inactivation. Supplementing chlorination with a pre-ozonation step slightly increases cancer illness and death. In the case study, this is due to the increased formation of bromate, whose oral cancer slope factor estimates exceed the oral cancer slope factor values for the other DBPs. While the concentrations of compounds like dibromochloromethane, bromoform, and chloral hydrate are also increased, their MLE cancer slope factors range from 3.4E-4 to 4.1E-2, and their

concentrations are increased from as little as 14% to just over 4-fold; the bromate concentration (MLE oral cancer slope factor of 3.2E-1) is increased from values below the detection limit (0.5 µg/L) to values exceeding 4.0 µg/L.

Capital and operational costs incurred by the ozone pretreatment technology are substantial in absolute terms. Nonetheless, the case study results suggest this technology yields substantial health benefits per dollar invested. CE ratios for the ozone pretreatment technology (Tables 6-19 and 6-20) have expected values ranging from approximately $2 per QALY for the AIDS subpopulation to $4000 per QALY for the general population. Furthermore, the graphs in Figures 6-3 and 6-4 show that the upper bounds for these two values are highly unlikely to exceed values of approximately $25 and $20,000 per QALY for the AIDS and general populations, respectively. For the total population (the AIDs subpopulation and the general population together), the CE ratio for this technology has an expected value of approximately $1,500 per QALY. All of these values are favorable in light of the ranges outlined by Kaplan and Bush (1982) (see Table 7-1). While the establishment of an ozone pretreatment facility would require an initial financial outlay, the treatment option would reduce the total QALY cost associated with anticipated levels of risk for simultaneous exposures to both microbes and DBPs, although most of the benefits, as measured in terms of QALYs, stem from the former.

7.2.2. Results: Baseline vs. Baseline Plus In-Home Filters. Unlike the ozone pretreatment technology, in-home filters are not assumed to affect DBP concentrations in tap water. This can be seen in Table 6-17 where no changes in either event counts or QALY costs are calculated for the DBP health effects. All benefits therefore stem from a reduction in morbidity and mortality associated with *Cryptosporidium* infection (Table 6-17). Since it is assumed that in-home filters

completely eliminate *Cryptosporidium*, QALY costs associated with these infections and their sequale are reduced to zero by this technology. As with the ozone pretreatment technology, these benefits are substantial, although the bulk of the benefits (measured in terms of QALYs) reflect a reduction in mortality, with a much smaller (although not insignificant) value for reduced morbidity. It may be notable that Table 6-17 shows that the opposite is true for the event counts (i.e., the number of morbidity events for this population are much higher than the mortality events); thus the value placed on mortality by the calculation of lost QALYs reflects the severity of the outcome.

Because the benefits for this technology reflect the elimination of *Cryptosporidium* from tap water, the estimated cost-effectiveness ratio for this technology depends heavily on many of the same factors that influenced the results of the ozone pretreatment assessment. Influential parameters include the source water oocyst concentration, the infectivity parameter, and the conditional probabilities of morbidity and mortality following infection. Because of the uncertainty in these parameters, the 90th percentile value of the QALY cost reduction accrued by the in-home filter technology exceeds the median estimate of this parameter by a factor of 2 to 3. The true uncertainty of this result is most likely to be even greater since the case study did not quantitatively characterize the uncertainty in the efficacy of the home filter, but instead assumed that this technology is certain to be 100% effective.

The CE ratio for in-home filters is approximately $150 to $175 per QALY (Tables 6-19 and 6-20). This ratio is well within the range of acceptable values outlined by Kaplan and Bush (1982) (see Table 7-1). It is also far more favorable than the total population CE ratio of the ozone pretreatment technology (approximately $1,500 per QALY). The home filter technology

has a highly favorable CE ratio despite its relatively high per-person technology costs (several thousand dollars, compared to approximately $20 per person for the ozone pretreatment technology) because it can be targeted to those members of the population at greatest risk. On the other hand, the AIDS-subpopulation CE ratio for the ozone pretreatment technology is far more favorable (approximately $2 per QALY) than the $150 cost-effectiveness ratio for the in-home filter technology, the beneficiaries of which are limited to the AIDS subpopulation. This difference does not imply that home filters are inefficient (i.e., a bad investment). As noted in Section 6.5.2, implementation of the ozone pretreatment technology reduces the residual risks that can then be eliminated by home filters; if both technologies were in place, the cost-effectiveness of the in-home filter technology would remain favorable, with a CE ratio of approximately $600 per QALY - well within the "acceptable" range specified by Kaplan and Bush (1982) in Table 7-1-1.

Several simplifying assumptions were employed in the case study application of in-home filters: 1) the reverse osmosis in-home system completely removes protozoa and protozoan oocysts, 2) as a result of preventing *Cryptosporidium* exposures to the susceptible population, essentially no deaths result from sequale of *Cryptosporidium* infections, 3) the reverse osmosis in-home system does not eliminate or reduce any of the DBPs, 4) estimates of the initial and installation costs of the reverse osmosis systems as well the annual costs adequately represent actual costs incurred, and finally, 5) an estimate of persons infected with AIDS is an adequate surrogate for all individuals with compromised immune systems. Changing these assumptions would affect the quantitative results of the analysis to some degree. Relaxation of assumptions 1 and 2, for example, would lead to increases in microbial morbidity and mortality, making the

home filter option less cost effective. On the other hand, relaxation of assumption 3 could lead to decreases in DBP-induced risks, making the in-home filter option slightly more cost effective. However, it is expected that the microbial risks would continue to overwhelm any affect on the results made by the DBP-induced risks. Any increase in the financial costs under assumption 4 would make very little difference because the positive change in QALYs that results for this subpopulation subjected to this technology are so large that even a doubling of the current cost estimate would be inconsequential to the CE ratio estimates. Finally, a broadening of assumption 5 to analyze all immunocompromised groups would increase technology costs and result in a positive change in QALY costs proportional to the increase in the subpopulation size. Again, because QALY costs are so much larger than the technology costs, it is likely that the CE ratio would remain favorable, but many factors related to human susceptibility, particularly in the immunocompromised subpopulation would have to be investigated. It is possible, for example, that substantive changes in influential factors such as the number of microbial-related deaths could significantly impact the results of the analysis.

7.3. PERSPECTIVE OF THE LOCAL WATER SYSTEM PURVEYOR

Use of the CRFM should be beneficial to the local water purveyor who must evaluate treatment options. The CRFM may be useful at the local level for the evaluation of treatment options needed for safe water and for compliance with new regulations under the Safe Drinking Water Act (SDWA) and its amendments (see Section 2.2). For most public water supplies serving populations over 10,000, there will be new requirements to filter and/or disinfect the water. These options have different technology costs, but also differ in terms of their efficacy for removal/inactivation of microbes (particularly *Cryptosporidium*) and in terms of DBP formation

and resulting concentrations. In addition to making comparisons across different types of technologies, the CRFM can be applied to evaluate within system changes such as variations in disinfectant contact time, gradations of disinfection concentrations, and differences in residual concentration. The application of the CRFM could help in the comparison of technology costs to a wide range of potential health impacts on the population served.

To reduce the uncertainty and increase the level of confidence in choosing among treatment options, the local purveyor must carefully evaluate many variables. One of these is the source water quality, specifically including the identification, quantification and viability of microbial content that will contribute to any microbial risk. Other factors that affect microbial content or treatment system performance, such as the impacts of mechanical treatment failures or operator errors, seasonal variations, droughts, and floods, may also need to be factored into the analysis. The local purveyor must also evaluate the source water for contaminants that may predispose the formation of DBPs (e.g., total organic carbon and bromide levels). These DBPs must then be identified and quantified. Additional efforts on the part of local purveyors should include a continual assessment of the population to be served and the consideration of specifically susceptible subpopulations.

While, for example, an ozone pretreatment/post chlorination option may be more cost-effective than other options such as the use of in-home filters, the funds planned for construction of a treatment facility may not immediately be available. The results of a CEA, however, may stimulate local governments to more carefully weigh the expected health outcomes against anticipated financial outlay. It is possible that specific and relatively inexpensive alternatives may provide dramatic decreases in risk in limited subpopulations. The example in the case study of a

point-of-use filtration device for the immunocompromised represents one such cost-effective option for the reduction of microbial risk for a specific subpopulation.

7.4. PERSPECTIVE OF THE NATIONAL RISK MANAGER

Use of the CRFM should also be beneficial to risk assessors and managers at the national level who must develop data and draft regulations. From the perspective of the national risk manager, the case study can be used to recognize which parameters and assumptions most affect analysis results, while identifying data gaps and uncertainties. Stage 1 of the negotiated rule-making by EPA and industry (see Section 2.2) consists of the promulgation in 1998 of the Disinfectant/Disinfectant By-Products (D/DBPs) rule and the Interim Enhanced Surface Water Treatment rule (IESWTR), which would further reduce exposures to specific DBPs and enhance protection from pathogens, especially *Cryptosporidium*. The CRFM set forth in this document can help provide a sound scientific basis for determining whether or not to go beyond the November 1998 Stage 1 DBP rule (e.g., 80 µg/L for Trihalomethanes [THMs]; 60 µg/L for 5 haloacetic acids [HAAs]; 10 µg/L for bromate) to additional regulations for DBPs or microbes. The CRFM can be tailored to determine and evaluate the effect of changing variables within a treatment process such as, the amount of disinfectant used, the length of contact time, or changing the order in which disinfectants or filtration procedures are applied. The Information Collection Rule (ICR) is a nation-wide sampling program for the collection of occurrence and treatment data. The ICR will generate empirical data on the microbial and DBP concentrations that are produced by specific treatment trains with detailed information on the source water characteristics; these data will be useful in future CRFM studies.

The present case study suggests that microbial risks have the greatest impact on the overall risk of morbidity and mortality associated with these treatment options under the conditions assumed for this analysis. However, the sensitivity analysis (Tables 6-15, 6-16 and 6-18) indicates that microbial risk assumptions, including infectivity and morbidity, are largely responsible for the uncertainty of the case study results. It follows that risk assessors and managers at the national level should encourage further investigation of microbial parameters, including the efficacy of disinfection strategies, the infectivity parameters for microbes of concern, and factors that may influence secondary transmission among the affected population. The lack of adequate methods to identify and quantify infectious *Cryptosporidium* oocysts is largely responsible for the uncertainties of these parameters.

Nation-wide variations in geography, rainfall, land use, and variation in the size of treatment facilities, local economic conditions, and serviced-population size and characteristics indicate that assumptions made about treatment needs will vary substantially across localities, even among those that are close in proximity. When generalizing the CRFM to larger regions, careful assumptions must be made about parameters such as qualitative and quantitative differences in microbial content, total organic carbon, and bromide levels (for ozone treatment) in the source waters.

Another consideration is the effect of system failures on the CRFM results. Although treatment failures, leading to microbial outbreaks, are not included in the present case study, it is likely that different treatment alternatives will have different failure probabilities over the life of the plant. An outbreak would increase the number of microbial health events and thus influence the CRFM findings. This case study suggests that research into alternative forms of disinfection

should focus on the degree to which alternatives control microbial risks, although DBP formation may be important in some circumstances.

EPA believes that the proposed CRFM will assist the Agency in determining the balance between adequate water treatment to control and minimize microbial risk and the creation of unacceptably high levels of countervailing risks from DBPs. The CRFM presented here is intended to support and strengthen traditional and existing risk assessment and risk management activities. Use of the CRFM for this environmental problem provides not only a comprehensive method for analyzing the impacts of a public health intervention, but is also a vehicle for the identification of the most important data gaps and uncertainties as a guide for future research planning.

8. RESEARCH NEEDS

One of the outcomes of the application of this approach is the identification of significant data gaps which influence the outcome of the decision analysis. Completion of comparative risk assessments for treated drinking waters necessitates a multidisciplinary approach. The research needs that arise from applying this method will include the following areas: drinking water treatment technologies, infectious disease assessment, toxicology, epidemiology, statistics, risk assessment, and decision analysis. Research needs that are a high priority based on the results of the case study are underlined.

Drinking Water Cost Effectiveness Analysis

- Improved estimates of morbidity and mortality risk from *Cryptosporidium* among normal, healthy individuals and among members of the AIDS subpopulation.
- Improved assessments for valuing disease state outcomes, particularly mild-to-severe disease and significance of duration.
- Better characterization of the types, durations, severity of health conditions and the values associated with these such as productivity costs and remedial costs.
- Preferences for health endpoints related.
- Development of a standardized inventory of medical costs and other costs (e.g., those of the parents of a developmentally disabled child) so that a common approach and values can be used.
- Development of risk communication strategies that stress risk-risk trade-off.

Drinking Water Treatment Technologies

- Identification of factors that influence the formation and persistence of DBP in treated drinking waters.
- Development of technologies to control and minimize disinfection by-products (DBPs) generated by common disinfection practices.

- Improved assessments of microbal efficy of drinking water treatment systems.

- Optimization of conventional treatment techniques for the removal of *Cryptosporidium*.

- Control of microbial regrowth in distribution systems relative to disinfection techniques.

- Evaluation of the effectiveness of alternative treatment techniques, including small systems, for microbial control and DBPs.

- Evaluation of failure of drinking water treatment systems including smaller municipal systems and in-home filters. Identification of frequency, duration and magnitude as well as resulting concentrations of microbial agents and DBP in the treated water that results from these failures.

- Increased information on DBP levels and microbial efficacy associated with other plausible water treatment options.

- Increased data on performance of in-home filtering systems, including effects on DBP concentrations.

Infectious Disease Assessment for Drinking Water Agents

- Development of methods for detecting and measuring *Cryptosporidium* concentrations and development of methods for assessing the viability/infectivity of *Cryptosporidium* in drinking waters.

- Identification of methods for assessing the infectivity of *Cryptosporidium*.

- Identification and characterization of populations at increased risk for waterborne illness.

- Improved estimates of the initial conditional probability associated with the progression of different stages of cryptosporidiosis, conditional probability of progression to mild illness given disease, and conditional probability of progression to severe illness given mild illness.

- Development of a dynamic population transmission model to evaluate person-to-person spread.

- Determination of waterborne endemic disease agents, incidence and prevalence, and approaches to reduce population exposures.

- Human health data and occurrence data on emergent pathogens.

Cancer and Reproductive/Developmental Epidemiology

- Improvement of the existing literature base for all adverse effects of concern in terms of both quality and quantity, requiring continued Agency financial support; studies that are designed to collect information on source water quality, distribution system characteristics, type of disinfectant used, and levels of specific chemical DBPs should be especially encouraged.

- Thorough evaluation of the findings from the existing epidemiologic studies in conjunction with data on the toxicology and metabolic fate and transport of the major DBPs, to evaluate the biologic plausibility of the observed associations while ruling out the contributions of bias and confounding.

- Development of more accurate and precise methods of exposure assessment must be developed, to construct better individual exposure histories. This includes methods for better measurement of occurrence levels of contaminants as well as a person's likely exposure to them. Recently completed studies can be evaluated for their potential for acquiring more refined exposure information.

Toxicology of Individual and Mixtures of DBP

- Completion of the qualitative and quantitative carcinogenic risk evaluation for DCA, TCA and chloral hydrate.

- Additional information about the mechanism(s) of DBP toxicity; studies designed to determine the modes of action are needed to provide insight into how individual DBPs in a mixture may elicit toxicity at high versus low concentrations.

- Additional information about DBP toxicity in children.

- Additional information about the non-toxic biochemical effects of very low doses of DBPs.

- <u>Better input data on the cancer, reproductive and developmental risks related to DBP exposure through drinking water in order to confirm or refute the causal nature of exposures, identify risks of concern, and get realistic dose-response estimates.</u>

- Better characterization of risks posed by DBP mixtures.

- Reconciliation of IRIS' use of data from corn oil gavage studies for the establishment of carcinogenic potency with the EPA OW's SAB 1990 recommendation that carcinogenicity data from corn oil gavage studies may be used for classification (weight-of-evidence) purposes, but not for quantitative estimation of risk.

- Development of chemical mixtures approaches for the estimation of nonadditive effects. Development of a methodology for performing individual hypothesis tests for additivity at specific mixture points including the additional steps necessary to provide an appropriate framework for risk assessment.

- Quantification of the significance of non-ingestion exposure routes.

- Identification of and assessment of individual and collective toxicity of unknown DBP.

- Identification of structural elements that influence the results of the Quantitative Structure Activity Model applied to unknown DBP.

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