M/DBP Stage 2 Federal Advisory Committee (FACA2) Microbial Risk

MEETING SUMMARY

Meeting #4

September 8-9, 1999
Washington, DC

Final
November 24, 1999

CONTENTS

I Introduction

In September 8-9 EPA held the fourth meeting of the Stage 2 Disinfection Byproducts and Long-Term 2 Enhanced Surface Water Treatment Rules (MDBP) Federal Advisory Committee (FACA). This meeting focused on risks from microbial pathogens. [See Attachment I.a for a list of meeting participants.]

After introductions, mediator Abby Arnold, RESOLVE, reviewed the objectives of this meeting:

- Provide a framework to evaluate data on microbial risk in a regulatory context;
- Introduce data on microbial occurrence;
- Review current studies of dose-response and epidemiology of microbial disease stemming from drinking water;
- Describe how EPA characterizes the risk implications of different regulatory options; and
- Identifies key questions for the TWG to address.

The Committee approved the agenda as proposed [See Attachment I.b.] This meeting report summarizes the discussions and next steps from this meeting.

II Framework for Microbial Risk Analysis in Regulatory Development

Stig Regli, EPA, provided an overview of (1) how different types of information on microbial risk influence regulatory decision making, and (2) the process EPA will use in assessing microbial risk. [See Attachment II.]

Under the Safe Drinking Water Act (SDWA) EPA must publish Maximum Contaminant Level Goals (MCLGs) at levels at which "no health effects occur and which allows for an adequate margin of safety." EPA must promulgate Maximum Contaminant Levels (MCLs) or treatment technique requirement as close to the MCLG as is "technically or economically feasible." The level at which EPA sets MCLs or treatment technique requirements is influenced by a regulatory impact analysis which characterizes the level of risk, including risks to sensitive subpopulations.

Microbial risks are generally regulated through a treatment technology requirement. Monitoring pathogens at very low levels requires many samples and with very large volumes of water. Pathogen occurrence can be highly varied and analytical methods are constrained by their relatively low sensitivity, accuracy, precision, timeliness and cost. Therefore, a treatment technology standard based on the level and effectiveness of treatment methods is used instead of an MCL.

MCLGs of zero currently exist for *Giardia lamblia*, viruses, *Legionella*, and *Cryptosporidium (Crypto)*. Current treatment technique requirements for pathogens include:

- Under the **Surface Water Treatment Rule**: all systems must achieve at least 3 to 4 log removal/inactivation of *Giardia*/viruses, demonstrated by technology usage, turbidity performance criteria, and design and operation criteria.
- Under the **Interim Enhanced Surface Water Treatment Rule**: filtered systems must achieve at least 2 log *Crypto* removal demonstrated by technology usage and meeting turbidity performance criteria.

Microbial pathogens have unique characteristics as compared to DBPs:

- Pathogen occurrence is difficult to characterize because not all organisms of concern are infectious, concentrations in water are highly variable, and analytical methods are not highly accurate;
- Secondary spread (person to person) of the infection can be significant;
- Immunity to illness can be highly variable and host dependant; and
- Reporting of pathogen infections is infrequent and sporadic.

Types of information that influence regulatory decisions includes occurrence, dose-response and epidemiological data. Because of difficulty in measuring low levels of pathogens in water, concentrations in finished water are generally extrapolated from source water occurrence and treatment effectiveness

data. Sources of occurrence data include the ICR, Supplement Surveys and other research. The analytical method for *Cryptosporidium* used in the Supplemental Surveys is better than that used in the ICR, however, it does not assess viability.

Data included in the Supplemental Surveys includes systems not covered under the ICR. While there are no Agency-wide risk assessment guidelines for microbial risks (as there are for cancer and DBP risks), methodologies are available for conducting assessments. Any risk assessment that EPA conducts to support the development of the LT2ESWTR will be peer reviewed.

Regli reviewed how various types of occurrence data may influence regulatory decisions:

- **National source water distributions of Giardia, Crypto, viruses and indicators** may indicate potential risk and the percentage of systems that may need treatment beyond that required by the SWTR and IESWTR. This data is also used in the national regulatory impact analysis.
- **Source water occurrence for utilities with poorest water quality** (magnitude and variability) may indicate potential risk and extent to which existing rules and technologies in place may not be sufficiently protective, and the extent of monitoring needed to characterize risk at the utility level.
- **Source water occurrence in unfiltered systems** may indicate potential risk and extent to which additional treatment may be needed in these systems.
- **Occurrence by water body type** (e.g., rivers versus lakes/reservoirs) may suggest different treatment requirements based on water body type.

Issues associated with interpretation of occurrence data include:

- Low recovery and high variability of method performance for pathogens,
- Different methods are used in different studies, and
- Uncertainty in how to interpret occurrence data. (What fraction of protozoa are infectious and to what extent? To what degree and extent are viruses pathogenic?)

Dose-response data for pathogens are used to support the MCLG and are also used in predicting probability of infection from ingestion in estimating national risk. Existing models assume that ingestion of one protozoa or virus has some probability of causing infection. Dose-response information may indicate the extent to which different strains of an organism may be infectious and may provide data for estimating probability of illness in the infected host. The availability of data influences the confidence in risk estimates. The dose-response data base does not represent the national population (e.g., does not include sensitive sub-populations) and all pathogen strains (e.g., strains used in studies may not reflect infection rates of all the strains in the environment.)

Epidemiology data on outbreaks may indicate the relative significance of different causes of waterborne disease (e.g., problems with treatment vs. distribution system problems.) Epidemiology data will help identify organisms of concern as well as areas of treatment that should be strengthened (e.g., the Milwaukee outbreak brought Cryptosporidium to national attention.)

In assessing microbial risks, EPA will consider all available data and formulate an interpretation of pertinent risks. EPA will submit this interpretation to the MDBP Stage 2 FACA, the Science Advisory Board, and the Drinking Water Advisory Committee for discussion and feedback. Regli explained that the risk assessment will be available in a piecemeal fashion, beginning in December 1999. In December, EPA anticipates that enough data will be available to evaluate risk levels from different water body types.

Following Regli's presentation the following points were made:

- Similar intervention studies results in surface and ground water systems may indicate that most microbial risks are distribution system related.
- In response to a question from a FACA member, Regli explained that, as compared with the Stage 1 rule development, there is now a greater amount of occurrence data with dose response curves for *Crypto* available and the complexities of interpreting the data are better understood.

III Introduction to ICR Microbial Occurrence Data Analysis

Mike Messner, EPA, provided an overview of the data analysis of microbial occurrence in the ICR data [See Attachment III]. Messner reviewed the process used for collecting, analyzing, and storing the ICR microbial occurrence data. Some analysis of the microbial occurrence data is likely to require complex statistical treatment.

Analysis of protozoan occurrence data is difficult because (1) low recovery of the ICR method (only a fraction of the protozoa are counted and there are a large number of zero counts), (2) variable volumes analyzed, and (3) discrete (counting) nature of pathogen measurement. Other complex issues include stratification of water type or region, and identification of indicator variables such as coliform or turbidity to predict protozoan concentrations.

In November, 1998, EPA held a Statistics Workshop[(1)] to address how to treat zeros in the ICR data and how or if to adjust for low recovery rates. Substituting methods were considered. However experts recommended that non-detects remain as zeros in the data base. Messner reviewed the differences in statistical analysis between chemical and protozoa measurement. Variability is high in the measurement of protozoa, even under ideal circumstances, because the number of protozoa in each sample is a discrete number and not a concentration measurable to a very low detection level. Therefore confidence intervals are much larger with protozoan counts than when measuring chemical concentrations.

Source water occurrence is measured in the ICR because the protozoan detection method is not very sensitive -- measuring occurrence in finished water would lead to very low detection. Messner reviewed other difficulties in determining occurrence from ICR data:

- Volumes analyzed are not exactly known and volume analyzed vs. volume sampled is different.
- False negatives - cysts and oocysts often escape detection.
- False positives -- misidentification of other bodies are counted as cysts or oocysts.
- Not all organisms counted are viable and infective.
- Detention time is variable.

In the Lab/Field Spiking Study, spiked samples were analyzed along with ICR samples to measure the accuracy/recovery of the ICR method. The mean recovery of the ICR method, the probability that a cyst/oocyst present in the volume analyzed will be counted, was calculated for *Crypto* (12%) and for *Giardia* (26%). The recoveries' coefficients of variation were estimated to be 75% and 65%, respectively. The coefficient of variation describes how much recovery varies from analysis to analysis compared to the mean recovery (the standard deviation of recovery divided by mean recovery). The term recovery, as used here, refers to the probability that a cyst or oocyst that is present in the volume analyzed will be counted. In response to a question, Messner explained that the certainty of the Lab Spiking Study is relatively high because of rigid quality assurance/quality control procedures used. The spike was added to the ICR sampled water and there was good agreement in volume analyzed between spike and control. Results may need slight adjustment for the original oocyst concentrations in matrix.

Messner presented an overview of the analysis of microbial occurrence from the first nine months of ICR data. Flowing streams contain statistically significant higher levels of *Giarida* and *Crypto* than reservoirs/lakes. Several participants noted that EPA should look at the distance of the reservoirs/lakes from flowing streams, residence times in reservoirs/lakes (which vary greatly) and system changes (such as pumping water from streams into reservoirs). A FACA member suggested that a greater understanding

of these trends and distinctions between water sources may lead to regulatory strategies that are focused on specific plant or source types. Because only the first nine months of data has been analyzed, Messner cautioned against basing any judgements on this analysis. A FACA member asked that any analysis contain a footnote explaining the amount of data contained (9-12-18 months).

Analysis of the ICR method shows that volumes analyzed are greater than expected, recovery is approximately as expected and occurrence levels for *Giardia* and *Crypto* are lower than anticipated. Ongoing data analysis activities include:

- summary charts and tables,
- exploratory data analysis (indicator variables, stratification, development of statistical models),
- estimate parameters for each source water,
- occurrence probability (presence/absence), and
- tiered Bayensian analysis (distribution of distributions).

Messner closed by offering that EPA would sponsor another "mini"-workshop on statistical methods for analyzing occurrence data, if the FACA desires.

Following Messner's presentation the FACA members raised the following points:

- In response to a question, Messner explained that for a one liter sample a zero result is almost as likely to represent a true concentration of 1 to 10 as zero because of low recovery. In 90% of surface water samples results were zero for *Crypto.*
- A FACA member suggested that instead of a workshop, one option is for the TWG to develop a recommendation to the Committee on how to handle statistical questions surrounding analysis of occurrence data (including low recovery and non-detects). The recommendation from the TWG could be a single strategy or several alternative methods and their strengths and weaknesses.
- A FACA member noted that the use of source water monitoring may undervalue watershed protection programs. Lumping water bodies into broad categories such as rivers versus reservoirs/lakes may reduce the FACA's ability to identify differences between management activities and differences between watershed sizes. ICR data, however, was designed to yield national averages, not site specific analyses.
- A FACA member remarked that the TWG may be able to tease out subcategories of water treatment plants by watershed protection activities and retention times to see whether these characteristics influence the number of non-detects.
- A FACA member commented that the ICR is likely to underestimate occurrence. One approach is for the TWG to develop an estimated range by assuming that ICR occurrence data is valid (no miscounting) and assign some number of non-detects (zeros) a number. This would represent a high end estimate of occurrence and would give high and low boundaries for possible occurrence when compared with the unadjusted ICR data.
- EPA and the FACA are faced with the practical problems of identifying how to use the ICR data, as well as additional occurrence data, with the health effects data to guide regulatory options development. Remaining questions include: Does this data lead to regulatory strategies that address risk differences? Can data distinguish between systems with higher and lower levels of risk?
- EPA will use all available data in its cost/benefit analysis. The national estimate of risk will be used to estimate the cost/benefit of regulatory options. This estimate does not direct the regulatory option that will be chosen, but it is one method of evaluating regulatory options.

IV Endemic Risk from Pathogens in Drinking Water

Jack Colford, UC Berkeley, presented an overview of the epidemiology of endemic risks from pathogens in drinking water [Attachment IV]. Colford began by presenting the background issues and terms used in discussing microbial risk including the difference between endemic (i.e., background) and epidemic (i.e.,

detected through surveillance) disease. Colford reviewed the issues surrounding the use of serology for estimating exposure. Serology and serological tests look for antibodies (i.e., proteins for fighting specific pathogens) in blood serum as an indirect measure (or "footprint") of prior exposure.

There are many types of pathogens that can cause waterborne illness, including viruses, parasites, and bacteria. Colford described the types of studies used to investigate waterborne disease:

- Cross-sectional
- Case-control
- Ecologic (grouped data)
- Time-series
- Cohort
- Intervention Trial

Colford also presented results from two intervention trial studies conducted by Pierre Payment:

- In 1991, Payment found that 34% of the excess illness in the group drinking their normal water was due to their exposure to drinking water.
- In the 1997 Payment study excess risk was associated with the distribution system.

Results from several studies are expected in the next year:

- Australia Water Quality Study (an intervention study);
- Food-Net survey of drinking water habits and gastrointestinal disease (CDC);
- California Water Intervention Trial (pilot). Full scale expansion scheduled to begin at two additional cities (one groundwater, one surface water in the next year);
- Case-control study of the association between Cryptosporidium and drinking water among non-immunocompromised persons in the San Francisco Bay Area; and
- Boston serological study for specific pathogens.

Colford, responding to a question from a FACA member, stated that there are more epidemics from waterborne than from foodborne *Cryptosporidium*. Waterborne epidemics tend to involve larger numbers of people. The correlation between epidemic and endemic disease is not understood. Colford provided a list of studies of endemic risk from drinking water and a list of references (see Attachment). In the discussion following his presentation Colford made the following points:

- After infection with *Crypto*, human beings produce multiple antibodies. Several are under investigation as possible research tools. It is not known which anti-*Crypto* antibodies, if any, confer protective immunity.
- Children, in general have more positive serum tests than adults.
- Serology does not distinguish between routes of exposure (e.g., water, air, person-person).
- The relative contribution of infection from waterborne and foodborne sources is not known.

V ICR Supplemental Surveys of Microbial Occurrence

Heather Shank-Givens, EPA, presented the first quarter/preliminary results from the ICR Supplemental Surveys [Attachment V.a]. The primary objectives of the Supplemental Surveys are to (1) determine national protozoan distributions for large, medium, and small systems for use in regulatory impact analysis and (2) compare protozoan distributions between large, medium and small systems. The Supplemental Surveys include an improved protozoa method and information on small systems.

Shank-Givens reviewed the basic survey design, parameters and geographical locations of surveyed plants. Data from the surveys will be compatible for comparison with ICR data.

Data delivery schedule:

March -- August 1999	6 months of large/medium 4.5 months small system data	October 29, 1999
March -- November 1999	9 months of large/medium 7.5 months small system data	January 28, 1999
March 1999 -- February 2000	**12 months large/medium** 10.5 months small system data	April 28, 2000
March 1999 -- April 2000	**12 months small system data**	July 28, 2000

Shank-Givens presented preliminary results from Method 1622 performance data for *Crypto* and an update on the development and round-robin validation testing for Method 1623 for *Crypto* and *Giardia*. Method 1623 was implemented in the Supplemental Surveys in July 1999. [See Attachment V.b. for a comparison of ICR Protozoa Method and Method 1622/23 analytical procedures]. The mean recovery for the ICR *Crypto* method was 12% while Method 1622, used in the Supplemental Surveys, achieved a mean recovery of 42%.

The first cut of analyses of the Supplemental Survey data include:

- Giardia distributions (Methods 1623);
- Indicator relationships (protozoa compared with turbidity, *E. coli*, etc.);
- Key comparisons (among system sizes/between source types); and
- Precursor distributions for medium and small systems.

FACA members raised the following points following Shank-Givens' presentation:

- Small system (serving fewer than 10,000) characteristics are often very different than medium or large size systems. EPA currently has occurrence and indicator data for medium and large systems. The ICR also contains some data on watershed characteristics for medium and large systems. The Supplemental Surveys include a random sample of small systems, a FACA member commented that there is large variation between different types of small systems.
- Protozoa data for small systems has not been collected because of expense. Because of the expense of detecting *Crypto* and other pathogens, EPA is attempting to identify indicator relationships.
- In response to a question, Shank-Givens explained that some utilities analyzed samples for both the ICR and the Supplemental Surveys. This data may be useful in using Survey data to answer questions on ICR.

VI Status of Additional Research on Occurrence of *Cryptosporidium*

Mark LeChevallier, AWWSC, presented an overview of additional research on *Crypto* occurrence by the American Water Works Service Company, and other research laboratories [Attachment VI.] LeChevallier forecasts that:

- New methodologies will permit more accurate assessments of Crypto in water.
- These data will permit assessments of public health and safety of drinking water.
- Research on disinfection (particularly UV) will provide improved treatment barriers.
- Molecular analysis of Crypto will yield better understanding of the organism in water.

LeChevallier presented an overview of the infectivity assay procedure (cell culture - PCR) for C. *parvum*. The procedure has been applied by AWWSC to monitor oocysts in raw and backwash water. The method will more directly estimate the health risk of *Crypto* in water. Methods are also being refined for tracking specific *Crypto* isolates, or genotypes. This DNA tracking of *Crypto* allows a researcher to follow a specific isolate within a watershed, outbreak, animal source, etc. Tracking isolates opens new opportunities for studying the ecology of *Crypto*.

AWWSC is currently monitoring finished water in 80 surface water plants monthly for 24 months, beginning in May 1999 and finishing in June 2002. In finished water, the cell culture PCR method had an average recovery rate of 37%. Data on turbidity and particle counts is collected daily in these plants. The purpose of the study is to determine if current treatment is adequate protect drinking water from *Crypto.* It is likely that regulatory and monitoring activities in the future will depend on the findings of current study.

In response to a question from a FACA member, LeChevallier explained that current analysis of infectious cysts will indicate whether current treatment is adequately protective. To date, one live *Crypto* oocyst was found in low turbidity water. Initial data on *Crypto* viability will be presented at the WQTC in November.

Project 488 is a source water assessment of pathogen concentration variability being undertaken by EPA and American Water Works Association Research Foundation. The study should be helpful in determining how to design a monitoring program for *Crypto* and *Giardia*. LeChevallier presented a project description, criteria for selection of plants in study, analytes, methods, labs, quality control program, and estimated error. Monitoring began June 1999 and will continue for 12 months with preliminary data available by the end of 1999. A complete data set will be available by the end of 2000, and a report will be ready by mid-2001.

LeChevallier reviewed ongoing research projects at the University of Florida (Joan Rose), the University of Arizona (Charles Sterling/Marilyn Marshall), Clancy Environmental Consultants, the Metropolitan Water District of Southern California, and the Philadelphia Water Department.

VII Summary of Waterborne Microbial Disease Outbreaks

Deborah Levy, CDC, presented an overview of the characteristics of the waterborne disease surveillance system, characteristics of surface water-related outbreaks in the US, the issue of under-reporting, and comparisons with the UK system [Attachment VII].

Characteristics of the US waterborne disease surveillance system include:

- Voluntary passive surveillance with annual solicitation of reports from state health departments.
- Two types of data: epidemiologic (required) and water quality (requested but optional)
- Unit of analysis is an outbreak (2 or more cases), except for chemical poisoning or amebic meningoencephalitis cases.
- Drinking water and recreational water are two types of waterborne outbreaks.

Levy reviewed data on etiological agents associated with waterborne outbreaks and data on water system deficiencies associated with outbreaks. Surveillance data are useful to:

- update the biology of etiologic agents and the epidemiology of outbreaks;
- determine epidemiologic trends;
- evaluate the adequacy of current technologies for providing safe drinking water and recreational water; and
- establish research priorities and assist in improving water quality regulations.

Factors that affect whether waterborne disease outbreaks are recognized and investigated by state and local public health departments include:

- Size of the outbreak;
- Severity of the disease caused by the outbreak;
- Public awareness that an outbreak might be occurring;
- Investigator's interest in studying the etiologic agent;
- Resources available to the health departments; and
- Routine laboratory testing for pathogens.

The actual number of waterborne disease outbreaks is unknown. The cause of under-reporting is under-recognition; and pathogens that are not routinely tested for in labs are unlikely to be identified. Levy presented the obstacles to reporting cases of waterborne disease and an overview of the UK waterborne disease surveillance system. The disease surveillance system in the UK is laboratory based, as opposed to reporting by state health departments or physicians to CDC in the US. Based on this comparison Levy concluded that:

- The characteristics of the surveillance system definitely affect the types of outbreaks that are identified, investigated, and reported.
- The UK and the US have very different systems, which in combination would provide excellent surveillance for waterborne disease. The US surveillance system depends on the patient going to the physician and the physician requesting the proper tests. The physician then needs to report the results of the tests to the health department. In the UK, decisions of what to test for are made by the Public Health Laboratories. Labs have direct computerized communication with the public health agencies and regional epidemiologists. All data are centrally located at the Communicable Disease Surveillance Centre.
- The UK can quickly make centralized decisions on what to monitor while in the US decisions are made by each state and by individual laboratories. The detection of an outbreak depends greatly on what labs are testing for, especially in terms of new pathogens of concern. The US system is more effective at detecting outbreaks of unknown etiologies because all that is required is for the health department to be alerted to the possibility of an outbreak by an individual or a physician. The UK system requires that a pathogen be identified before an outbreak will be recognized.
- In general, the UK definition of an outbreak is similar to the definition in the US. However, the UK system is less likely to detect outbreaks associated with recreational water usage. Water quality data are collected whenever possible in both systems if an outbreak is detected.
- Overall, a decrease in outbreaks associated with treatment problems at water utilities has been noted with more problems occurring locally and being associated with a building, restaurant, camp, etc. The majority of problems are treatment-related with additional problems being associated with distribution systems. These latter problems are more difficult to monitor and correct. The effectiveness of monitoring varies among states.
- At the FACA's request, Levy agreed to provide data on Crypto occurrence from the UK.

It is unclear how to account for the recent downturn in outbreaks detected. Levy expressed her belief that both waterborne and foodborne disease are underestimated.

VIII Overview of Dose-Response for *Cryptosporidium* and *Giardia* and Relative Risk

Dennis Juranek, CDC, presented data on the relative risks of fatality associated with *Crypto* and *Giardia* [Attachment VIII]. Overall risks from waterborne pathogens are relatively low, as compared with other risk factors (such as cancer, heart disease, or accidents) and are estimated to be many times lower than for foodborne pathogens. In estimates of risk levels, CDC assumes that everyone is at equal risk to waterborne disease. However, it is recognized that risks vary among water systems and that everyone is not at equal risk. CDC estimates 0.2 to 1.3 million cases of waterborne disease per year. If data from the

Payment study, which suggest that 10%-14% of gastrointestinal illness may be water related, are used to calculate an estimate, the estimated number of cases would be 30-50 million cases per year.

New research has led to the lowering of previous estimates of deaths from foodborne disease from 9000 to 5000 per year. The revision reflects data that indicate that death is less likely to occur from many pathogens than previously thought. Some of the foodborne pathogens whose mortality rates have been downgraded are also waterborne. Thus it is likely that the estimated number of deaths from waterborne disease (900 per year) will also be downgraded when available data are reanalyzed.

CDC FoodNet data indicates that there are about 370 million episodes of diarrhea/year in the U.S.. CDC estimates that 30%- 40% of these episodes are the result of foodborne disease. Compared with the number of foodborne disease studies, data and studies on the occurrence of waterborne disease are few. This is partly in recognition that foodborne disease poses a significantly greater public health problem in the U.S. than waterborne disease. The Payment studies in Canada represent one of the few recent attempts to estimate the amount of waterborne disease in the absence of an outbreak. Payment estimated that 14% of gastrointestinal illness in a community may be waterborne. If the 14% rate is applied to the 370 million diarrhea episodes per year, then more than 50 million episodes of waterborne diarrhea could be occurring each year. There are many reasons to suspect that 50 million is an overestimate, but there are equally compelling reasons to believe that 1 million episodes is an underestimate. Funding for waterborne disease studies that are intended to provide a better estimate of the microbial risks to humans has only recently become available. Completion of the microbial risk studies over the next 2-5 years should provide significantly better estimates of waterborne disease than are now available. Regardless of the outcomes of these studies, water will likely always be held to a higher standard of safety than other food items because producers have more control over the source and treatment of water [it does not come from other countries], consumers have no choice about the brand they receive, and unlike many other food items, consumers can not live without water.

Moreover, while many food items are distributed with a routine public health message that presumes contamination [handle with care, wash hands and counter tops after handling, cook well], water is delivered directly to the home with the public health message that it is safe.

Crypto transmission can occur through person-person, animal-person, water, food and environmental exposures to *Crypto*. There are different species of *Crypto* which infect different animal hosts (e.g., mammals, birds, fish, snakes). *C. parvum* is the species that commonly infects humans and other mammals. Recently two other species (*C. felis* and *C. maleagridis*) have been identified in immunosuppressed humans.

Two genotypes of *C. parvum* have been reported by several investigators. Genotype 1 infects only humans and cannot be transmitted to other animals. Genotype 2 primarily infects animals but can also be transmitted to humans. Waterborne outbreaks associated with both genotypes have occurred in the U.S. and the U.K. Other genotypes of *C. parvum* are likely to be reported soon.

All studies of oocyst susceptibility to water treatment (filtration, disinfection, etc) and tests of oocyst infectivity for humans have been done with *C. parvum* -- genotype 2. Human-dosing studies in healthy volunteers given *C. parvum*-genotype 2 have shown large variations in number of oocysts from different isolates that are needed to cause either infection or disease. As few as 10 oocysts of one isolate infected 50% of human volunteers while other isolates required a dose of 1100 oocysts to achieve the same number of infections.

Oocysts were stored for 4 to 6 weeks before they were inoculated into healthy non-immunosuppressed adults. Some immunity does develop; however, the length of protection is not known. 15-20 times more oocysts are needed to cause a second infection and second infections are milder. Immunity may protect against very low oocyst doses (1-10) of the same isolate; however, the degree immunity achieved against other isolates/genotypes is unknown.

Problems with current human infection studies include the age of innoculum and that in-vitro excystation tests of oocyst viability may not be an accurate indication that the oocysts being delivered in a dosing trial all have the same potential to infect a human or animal.

A single oocyst may be more likely to infect humans than a single bacteria. Juranek reviewed the life cycle of Crypto pointing out that the oocyst's wall offers substantial protection from the host's immune system and stomach acids for the four infectious sporozoites inside. Enteric bacteria do not have the benefit of such protection and generally require doses in the 1000's and 10,000's to infect humans. *Crypto* oocysts do not open until they reach the small intestine where four organisms are released. These organisms are motile and penetrate the cells lining the intestine. Once in the cell, they position themselves in a unique location between the cell membrane and cytoplasm where the body's immune system and drugs have a hard time getting at them. The parasites then reproduce logarithmically; each dividing into 8 in the first round of merogony.

Exactly how *Crypto* causes disease is not known. While there is some damage to cells lining the intestine, most of the diarrhea is believe to be due to a malfunction in one or more chemical pumps that control fluid movement in and out of the intestine. The malfunction results in a disproportionate amount of fluid flowing from the body into the intestine producing a secretory diarrhea.

In response to a question, Juranek explained that estimates from the Milwaukee and other outbreaks indicate that the risk of secondary spread among adults is about 5% and can be as high as 20-30% if there is a diaper-age child in the house.

FACA members made the following comments:

- Studies in animals indicate that antibodies last for only short periods of time (months), and so, may be indicators of relatively recent exposure.
- There are two classes of antibodies: adults develop antibodies that are protective against infection, while children may develop partial immunity.
- Crypto infection may cause cell death and shorting of villi in the small intestine. Intestinal damage may be substantial in immunsuppressed people with chronic infection. Those infected with *Crypto* may not be able to absorb nutrients.
- Resistance to infection may be the result of cell mediated immunity stopping oocyst production, not antibodies.

Future research on the human genotype (e.g., infectious dose studies in humans and human immunologic response) and human versus animal genotype (e.g., prevalence in source water and prevalence in human population) will not be available in time for the FACA's consideration. A previous Floyd Frost 2-City Study showed that antibodies are present in populations using surface waters at levels double those using groundwater. A follow-up study now underway is collecting data in 15 cities.

IX Overview of Dose-Response for Viruses

Mark Sobsey, University of North Carolina, presented an overview of current knowledge on dose-response relationship for waterborne viruses, acquired immunity from prior exposure to viruses, sensitive sub-populations, and ongoing research in this areas, as well as a summary of types of information expected to become available in the next 12 months [Attachment IX.]

There are a large number of enteric viruses that could be waterborne, including Hepatitis E, rotavirus, Calicivirus and others. Dose-response information exists for very few viruses. Data on waterborne outbreaks comes mainly from Asia and Africa and support the conclusion that the infectious dose of viruses is very low. Literature on the Norwalk virus is mainly high dose exposure, although there is some low dose data. However, these studies do not include serological tools used to identify infection and measured illness as the outcome. In response to a question from a FACA member, Sobsey explained

that it is difficult to judge how well the 6 or so well known viruses can be used to estimate the 150 or so that are not well understood. New viruses and new classes of viruses are constantly being identified and the "worst-case" is not known. Sobsey also explained that aerosol exposure from bathing and showering is a very effective mode of infection of the respiratory tract. However, this is known through toxicology data, not epidemiology.

Viral infection can lead to illness, sequella (i.e., other long term effects that appear after illness), and possibly death. Infections which begin in the digestive tissues can migrate to other sites, such as the central nervous system or liver. The genetic makeup of viruses determines how infective they are. Some people may be genetically more susceptible to particular viruses; genetically sensitive individuals may not produce antibodies to a virus. Antibodies produced by the body recognize and react to proteins on a virus. Changes in these proteins through genetic variation or "antigenic drift" reduce the ability of the body to recognize the virus.

Viruses can be inactivated through disinfection using chlorine, chlorine dioxide and ozone (if residual). However, they are more resistant to UV. Viruses measure 20 to 100 nanometers in length requiring the use of microfilters for removal. Viruses are transported through water by Brownian motion. Because of their small size viruses will not settle out of water unless associated with larger particles. Viruses are negatively charged, allowing for the use of positive coagulants. More research is needed on charge interactions to take advantage of the particular characteristics of viruses for their removal. Viruses are generally heat sensitive, however some strains are resistant to heat.

Additional points made during the presentation:

- Calciviruses are waterborne and foodborne and account for a large fraction of gastrointestinal illness.
- For some viruses the risk of secondary spread is substantial (as high as 50%). Rates of illness vary for different viruses between children and adults.
- Hepatitis E has a mortality rate of 1 in 3 in pregnant women, however, susceptibility varies profoundly between different groups. Infectious dose for Hepatitis E is not known, but is thought to be low.
- Some viruses can survive for long periods and are resistant to treatment. Hardiness of viruses in the environment varies greatly.

X EPA Considerations in Evaluating Waterborne Microbial Disease Risk

Stig Regli, EPA, presented a historical perspective on waterborne microbial disease risk including how EPA characterizes the risk implications of different regulatory options and

how risk is considered under the Safe Drinking Water Act (SDWA) [Attachment X].

Surface Water Treatment Rule

Under the 1996 amendments the Surface Water Treatment Rule (SWTR) EPA promulgated MCLGs of zero for *Giarida*, viruses, and Legionella. EPA set standards as close to MCLGs as considered technically and economically feasible, with intent to still be "protective". EPA characterized SWTR as reducing risk to less than 1 infection from giardiasis per 10,000 people per year, with infection used as a conservative indicator of illness. Limited source water data at that suggested that most systems would meet this risk level. EPA guidance recommended that systems with poor source water provide removal/inactivation greater than the 3 /4 log required under SWTR. However, it has been difficult to determine criteria for "poor" source water quality.

1996 Amendments to the SDWA

- EPA must set MCLGs at levels at which no health effects occur (with an adequate margin of safety.
- EPA must promulgate MCLs or treatment technique requirements as close the MCLGs as is "feasible" -- taking costs into consideration and considering sub-populations.
- EPA must conduct benefit cost analyses considering health effects in sensitive sub-populations.
- EPA may consider risk-risk tradeoff issues.

Final Interim Enhanced Surface Water Treatment Rule (1998)

Under the IESWTR EPA established; (1) an MCLG of zero for *Crypto*, (2) criteria established requiring systems to evaluate site specific risk/risk tradeoffs associated with DBP rule compliance, and (3) consultations with states on significant changes to disinfection practices.

Future Rules

Agency risk assessors will be expected to address or provide descriptions of:

- individual risk -- including central tendency and high end portions of the risk distribution;
- population risk -- estimate probable number of illnesses and percentage of the population with risk greater than specified levels (e.g. 10-4, 10-5, etc.); and
- risks to subgroups -- highly exposed or highly susceptible groups.

The following points were discussed following Regli's presentation:

- In response to a question from a FACA member, Regli explained that the basis for the current 10-4 risk level for microbial pathogens is that it appeared to be commensurate with the 10-4 to 10-6 risk level in the cancer guidelines. While the health goals for the Stage 2 rules are set by EPA, the FACA must define what options are technically and economically feasible. This risk level estimate is a way to define technical feasibility based on risk levels.

- In response to a question, Regli noted that the impacts on children, elderly, AIDs and other immuno-suppressed populations from a 10-4 risk level for healthy population is something that EPA, along with the FACA, will be trying to determine.
- In response to question regarding EPA's estimates of waterborne disease, Regli explained that three dose response curves for Crypto have been developed and that EPA with the FACA should characterize the possible risk levels for consideration.
- A FACA member suggested that the Committee consider applying the principle that any expensive technical solution would require a high confidence health in data be met.
- A cost of death will be established, based on the value of statistical life. EPA will explain the economics of this calculation for waterborne disease, if requested by the FACA.

XI Perspectives on Microbial Risks Beyond Diarrhea

Chuck Gerba, University of Arizona, presented an overview of hazard identification, exposure assessment, effects assessment, risk characterization, and risk management for microbes in drinking water [Attachment XI].

Quantitative risk assessments consists of:

1. Identification of pathogen of concern;

2. Dose-response data from humans;

3. Model infection probability;

4. Clinical data to estimate probability of disease and mortality;

5. Predict probability of disease from exposure; and

6. Validate model from outbreak data.

Gerba presented the findings of quantitative risk assessments done for several pathogens:

- Greatest uncertainty in estimating risk is associated with exposure;
- No dose-response threshold for enteric viruses and parasites or the infectivity is so low it should be considered one organism;
- Sensitive populations (i.e., those at greatest risk) represent 20% of US population and is increasing though aging and techniques for treatment of cancer;
- Sequelae are common and have a significant impact on the quality of life; and
- Treatment plan variability in pathogen removal affects long term risk -- i.e. the more polluted the source water the greater the need for treatment reliability. Reliability may be the main concern; disease incidence may be related to short events of low pathogen removal efficiency in plants.

Gerba identified pathogens of concern (possible present in drinking water) for various effects including cancer, nervous system disorders, birth defects, and endocrine disrupters, as well as diseases of various organs. Exposure to pathogens in the water always results in the risk of infection, disease and death. Existence of antibodies to a pathogen in an individual indicates previous exposure, but not necessarily immunity from infection or disease. Host responses to pathogens can include no infection, sub-clinical disease, and clinical disease. Clinical disease can result in mild, moderate, or severe illness or death.

Acquired immunity can be non-protective (indicative of past infection only), protective of re-infection (though not lifelong), or cause immune-mediated injury (autoimmune disease). There are no lifelong protective antibodies produced against many pathogens, and antibodies may not last the lifespan of an individual, leading to re-infection later in life. Two to three percent of infections lead to chronic sequelae (i.e., disease to occurs after infection) whether the initial infection was symptomatic or asymptomatic. Autoimmune diseases caused by waterborne microorganisms include rheumatoid disease, thyroid disease, and neural disorders. It is very difficult to link sequelae, including autoimmune disease, with initial cause. Autoimmune diseases are not currently tracked in any disease registry.

The following points were discussed following Gerba's presentation:

- In response to a question, Gerba explained that pathogens associated with conventional technologies are well known. However changes in treatment technologies will lead to shifts in the main pathogens of concern.
- European data is useful in identifying pathogens of concern but cannot be related to plant or outbreak data in the US.
- Gerba has participated in a report on plant failure mode research, which he offered to make available to FACA members.

XII Report from Technical Workgroup

Mike McGuire, MEC, updated the Committee on the activities of the TWG[Attachment XII]. The TWG has analyzed nine months of ICR data using the Primary Auxiliary Database (Aux 1) and expects to analyze and present 12 months of data at the October FACA meeting. The October presentation will include a characterization of the ICR baseline. The TWG will characterize the Stage 1 baseline for presentation at

the December FACA meeting. Analysis of the entire 18 months of data will be presented to the FACA at the January FACA meeting.

McGuire reviewed the analysis plan for ICR data and the data collection frequencies for analytes. The ICR included approximately 300 utilities comprising 500 plants. The ICR includes data on the type of source water (lakes, flowing streams, ground water) and intake location. ICR samples included influent, which could be either a single or mixed source, finished water for each plant, and distribution system. McGuire presented the National distribution of utilities and plants, ICR population distribution, and source water type. McGuire noted that high TOC levels in the Southeast can explain some unexpected data trends - called the "Florida effect". Based on the 9 months of data, McGuire presented the geographical distribution of TOCs, bromide, TTHM, BDCM, HAA5, bromate, and chlorite in surface water and groundwater utilities. McGuire noted that National trends in groundwater versus surface water plants cannot be extrapolated solely from ICR data because of the large differences between ICR and non-ICR utilities. However, surface waters generally have higher levels of DBP precursors than groundwaters.

XIII Next Steps

- At the FACA's request, Dr. Levy agreed to provide data on Crypto occurrence from the UK.
- A report on plant failure by Dr. Gerba is available to FACA members by request. For a copy of this report contact Detra Stoddard at RESOLVE by email [dstoddard@resolv.org] or phone (202) 965-6218.
- The FACA requested that the TWG prepare an overview of treatment technologies.
- All future presentations of data analysis should contain a qualifier footnote with the amount of data contained (9-12-18 months).

Adjourn

List of Attachments

I.a Meeting Participants

I.b. Meeting Agenda

II. Framework for Microbial Risk Analysis in Regulatory Development - Stig Regli, EPA

III. Introduction to ICR Microbial Occurrence -- Michael Messner, EPA

IV. The Epidemiology of Endemic Risk from Pathogens in Drinking Water -- Jack Colford, University of California, Berkeley

V.a ICR Supplemental Surveys: First Quarter Results -- Heather Shank-Givens, EPA

V.b Comparison of ICR Protozoa Method and Method 1622/23 Analytical Procedures -- Heather Shank-Givens, EPA

VI. Status of Additional Research on *Cryptosporidium* Occurrence -- Mark LeChevallier, AWWSC

VII. Surveillance for Waterborne Disease Outbreaks -- Deborah Levy, CDC

VIII. Overview of Dose-Response for *Cryptosporidium* and *Giardia* and Relative Risk -- Dennis Juranek, CDC

IX. Overview of Dose-Response for Viruses -- Mark Sobsey, University of North Carolina

X. Historical Perspective on Waterborne Microbial Disease Risk -- Stig Regli, EPA

XI. Perspective on Microbial Risks Beyond Diarrhea -- Chuck Gerba, University of Arizona

XII.a TWG Presentation to FACA Committee -- Mike McGuire, MEC

XII.b Draft Big Questions for TWG -- prepared by Mike McGuire, MEC, and Jennifer McLain, EPA.

---

[1] The meeting summary from the November 19, 1999 Statistics Workshop is available by contacting Morissa Young at RESOLVE by email [myoung@resolv.org] or phone (202) 965-6216.