Microbial Risk Assessment of Pathogens in Water

Glossary Dose-response assessment The determination of the relationship between the magnitude of exposure (dose) to a microbiological agent and the severity and/or frequency of the associated adverse health effects (response). - Exposure assessment Qualitative and/or quantitative evaluation of the likely intake of microbial hazard via all relevant sources or a specific source. - Exposure Concentration or amount of an infectious microorganism that reaches the target population, or organism usually expressed in numerical terms of substance, concentration, duration, and frequency. - HACCP: Hazard Analysis Critical Control Point A system that identifies, evaluates, and controls hazards that are significant for water safety. - Hazard A biological agent with the potential to cause an adverse health effect. - Hazard identification The identification of microbiological and biological agents capable of causing adverse health effects that may be present in water. - Hazardous event An event that may lead to the presence of a hazard in drinking water. - Health effects Changes in morphology, physiology growth, development or life span of an organism, which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects or other environmental influences. - Infection Colonization of a human (tissue) by a microorganism. - Infectious disease Colonization by a pathogenic microorganism leading to overt symptoms of disease. - Pathogen A microorganism capable of causing disease. - QMRA Quantitative Microbial Risk Assessment. - Risk assessment A scientifically based process consisting of the following steps: (1) hazard identification, (2) exposure assessment, (3) effect assessment, and (4) risk characterization. - Risk characterization The qualitative and quantitative estimation, including attendant uncertainties of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization, and exposure assessment. - Risk The likelihood of occurrence of an adverse health effect consequent to a hazard in drinking water. - Uncertainty Lack of knowledge about specific factors, parameters, or models. Uncertainty includes parameter uncertainty (measurement errors, sampling errors, systematic errors), model uncertainty (uncertainty due to necessary simplification of real-world processes, mis-specification of the model structure, model misuse, use of inappropriate surrogate variables), and scenario uncertainty (descriptive errors, aggregation errors, errors in professional judgment, incomplete analysis). - Variability Intrinsic heterogeneity in a population, process, or parameter. - Water Safety Plan (WSP) A management plan developed to address all aspects of water supply that are under the direct control of the water supplier focused on the control of water production, treatment, and distribution to deliver drinking water.

Definition of the Subject

Water can transmit infectious diseases . Water can be transport vehicle. A range of pathogenic microorganisms is shed into the water cycle by infected hosts (man or animal) and transported to new hosts by the water cycle. Water can also be a niche for (opportunistic) pathogens. These pathogens grow in water ecosystems (natural or man-made) and may infect humans that come into contact with this water. Management of the risk of waterborne disease transmission requires knowledge about the nature of the pathogens, their potential growth, fate and transport in the water cycle, the routes of exposure to humans and the health effects that may result from this exposure in the human population, as well as the effect of potential mitigation measures. The challenge is to combine all this knowledge into information that risk managers can use. Quantitative Microbial Risk Assessment (QMRA) has developed as a new scientific discipline over the last 2 decades as a transparent, science-based approach that allows the risk manager to use the best available scientific evidence as basis for risk management decisions.

Introduction

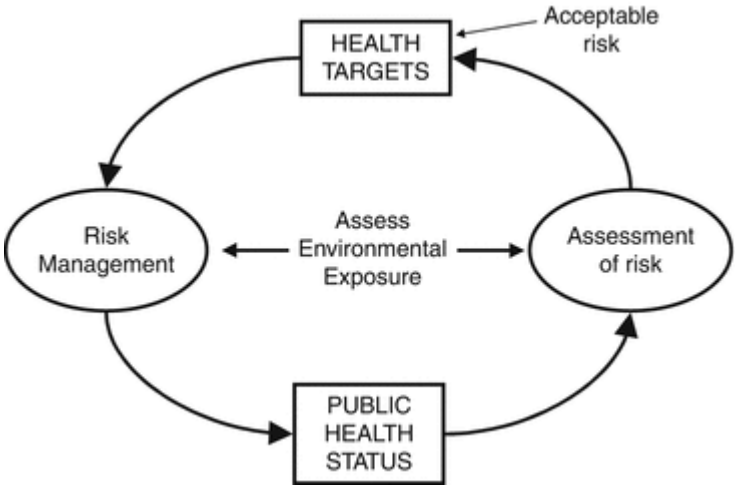
We run risks. We always have. From being eaten by lions, being slaughtered by a rivaling tribe, to being hit by a car. A principal objective of decision making has always been to reduce risks. From avoiding lions, building walls around cities to regulating traffic. To make wise decisions, it is important to have good information about risks. Risk assessment aims to aid decision makers by collating and evaluating this type of information. Risk assessment is increasingly applied in our society, for a wide range of activities: economy, finance, insurances, traffic, infrastructure, health, and environment. What all these activities have in common is that we want to reduce our risk and need to spend resources on mitigation measures. Our resources are limited, so we need to allocate them wisely and proportionally. Risk assessment helps to

keep proportions. Risk assessment as a formal discipline has emerged after World War II, paralleling the developments in air and road traffic, the nuclear power and chemical industries and the need to improve the safety of these activities. The process of risk assessment tries to determine the probability that a hazardous event will occur and the probable magnitude of the adverse effects that such an event will have. In the Netherlands, where a substantial part of the country lies below sea level and is protected against flooding by dikes, the height and strength of the dikes are based on assessing the probability of a storm event and the probable magnitude of the adverse effects of flooding part of the country.

In the health and environment arena, risk assessment science has developed over the last few decades. In environmental health , scientists try to establish the probability of exposure of humans to toxic chemicals or pathogens and the probable magnitude of the health effects of this exposure. Risk assessment has become a dominant tool in environmental policy-making, For chemical risks, this is well established (although not without debate [52]). Regulatory agencies are using chemical risk assessment to set standards for toxic chemicals in water. For risks of pathogenic microbes via water, the use of risk assessment was first proposed in the early 1990s [60]. The World Health Organization has been instrumental in the introduction of microbial risk assessment as a basis for safety management of the water we use for drinking, recreation, and food crop irrigation [73, 74].

The Safe Water Framework

An international group of experts, assembled by the World Health Organization, discussed the approach to assess and manage the health risk of pathogenic microorganisms in drinking water , recreational water, and wastewater reuse [7]. This group agreed that future guidelines for safe water and sanitation should integrate risk assessment and risk management into a single framework, the Safe Water Framework. The simplest form of the framework is shown in Fig. 1.



Microbial Risk Assessment of Pathogens in Water. Figure 1 Safe Water Framework for integrated risk assessment and risk management

The risk that is assessed and managed in this approach is a health risk. It is clearly an iterative cycle in which risk assessment is a basis for decision making in risk management. The four steps of the cycle are described in the next paragraphs, using drinking water safety as an example. In the World Health Organization (WHO) guidelines for the safe use of wastewater, excreta, and grey water [74], these same steps are used for assessing and managing the risk of these water systems.

Health Targets

Health targets are benchmarks for water suppliers, set by the regulator as part of their health policy. Health targets for drinking water are traditionally strict because of the large impact of contaminated tap water and the basic need for safe drinking water. That leads to the question of what level of health risk through drinking water could be tolerated, given the overall health status of the consumer population and the contribution of drinking water to the overall health risk of this population in relation to other routes of exposure, such as food, person-to-person or animal contact, recreational water,

etc. This is a question that typically needs answering on the level of the regulator, who can translate this information into a health target for drinking water, considering other factors such as relative contribution of drinking water-transmitted disease to the overall health burden and the economic climate.
The health target is the level of tolerable risk for drinking water , which could be expressed as the tolerable risk of infection through drinking water (i.e., risk of infection $<10^{-4}$ per person per year [61]) or the tolerable amount of disease burden (i.e., $<10^{-6}$ disability adjusted life years per person per year [31, 73]). The health target could be translated into water quality targets for pathogens (analogous to the toxic chemicals). In the latter case, rather than producing a standard and monitoring requirement for all pathogens that could be transmitted through drinking water, the use of a suite of "index pathogens" is advisable. Establishment of adequate control against this suite of pathogens should offer protection against the other known (and even unknown) pathogens.
It is emphasized that the health targets may be different in different health status situations. The question of what is a tolerable level of risk is a judgment in which the society as a whole has a role to play; the decision on the cost-benefit is for each country to decide [71, 73]. It is important that health-based targets, defined by the relevant health authority, are realistic under local operating conditions and are set to protect and improve public health. Health-based targets underpin development of Water Safety Plans [73] and provide information with which to evaluate the adequacy of existing installations, and assist in identifying the level and type of inspection and analytical verifications appropriate.

Risk Management

Managing the safety of drinking water has been the core business of water supply companies for more than a century. Over this period, risk management has evolved into a culture, with codes and specifications of good practice. In the last few decades, quality management systems have been used in the water industry to formalize these practices. Currently, water suppliers in several European Union (EU) countries are using a Hazard Analysis and Critical Control Points (HACCP) based approach for management of (microbiological and other) risks. The basic principles of HACCP are to understand the system and the hazards/hazardous events that may challenge the system and their (health) priority and to ensure that control measures are in place and functioning. HACCP-based systems typically focus on good practice and even more specifically on ensuring that good practice is maintained at all times. HACCP fits within existing quality management systems (i.e., ISO 9001 c.s.). HACCP is the risk management tool that is used in food safety. The Codex Alimentarius (FAO/WHO code for food safety) defines HACCP as a system that identifies, evaluates, and controls hazards that are significant for food safety [10]. The HACCP system is well established in the food industry.
Although there are many aspects of drinking water that are similar to food, there are also differences. Based on experiences of water suppliers with HACCP, the HACCP system has been refined and tailored for application in drinking water abstraction, treatment, and distribution in WHO's Water Safety Plan. The Water Safety Plan is described in the third revision of the Guidelines for Drinking Water Quality [73].
The principal components of the Water Safety Plan are:

- System assessment to determine whether the water supply chain (from source through treatment to the point of consumption) as a whole can deliver water of a quality that meets the above targets.
- Operational monitoring of the control measures in the supply chain that are of particular importance in securing drinking water safety.
- Management plans documenting the system assessment and monitoring, and describing actions to be taken in normal operation and incident conditions, including upgrade and improvement documentation and communication.

In the Water Safety Plan, the risk assessment question: "Do we meet the health target?" is answered in the System Assessment and the risk management questions "How do we ensure and demonstrate that we always meet the target?" and "How do we respond to incidents?" are answered in the Operational monitoring of control measures and the Management plans.
For an overview of the Water Safety Plan and its context, the reader is referred to the WHO GDWQ and the Water Safety Plan guidance documents that are published on the website of WHO Water, Sanitation, and Health.

Public Health Status

The primary objective of drinking water safety management is the adequate protection of public health. The incidence of

waterborne illness in the population or the occurrences of waterborne outbreaks are direct triggers for curative risk management. A more preventative incentive for assessing the water-related health risks and the installation of risk management is to demonstrate that the water supply is providing an adequate level of protection of public health.
The installation of health targets in national legislation and the risk management actions of water utilities should result in an improvement of the status of public health. Without addressing this, it is impossible to see if the health targets set and risk management actions taken are effective and if money spent for improving water supply results in a relevant health gain. This step in the process is the place where the health risk of drinking water can be compared to other routes of exposure and to other health risks . It allows comparison of the effort and resources put into the provision of safe drinking water versus resources allocated to manage other health risks.
The risk assessment and management framework is a circular process that can be run in an iterative manner. This fits well with the incremental nature of health decision-making, the efficient use of scarce resources, and the increase of information each time the circle is completed.

Risk Assessment

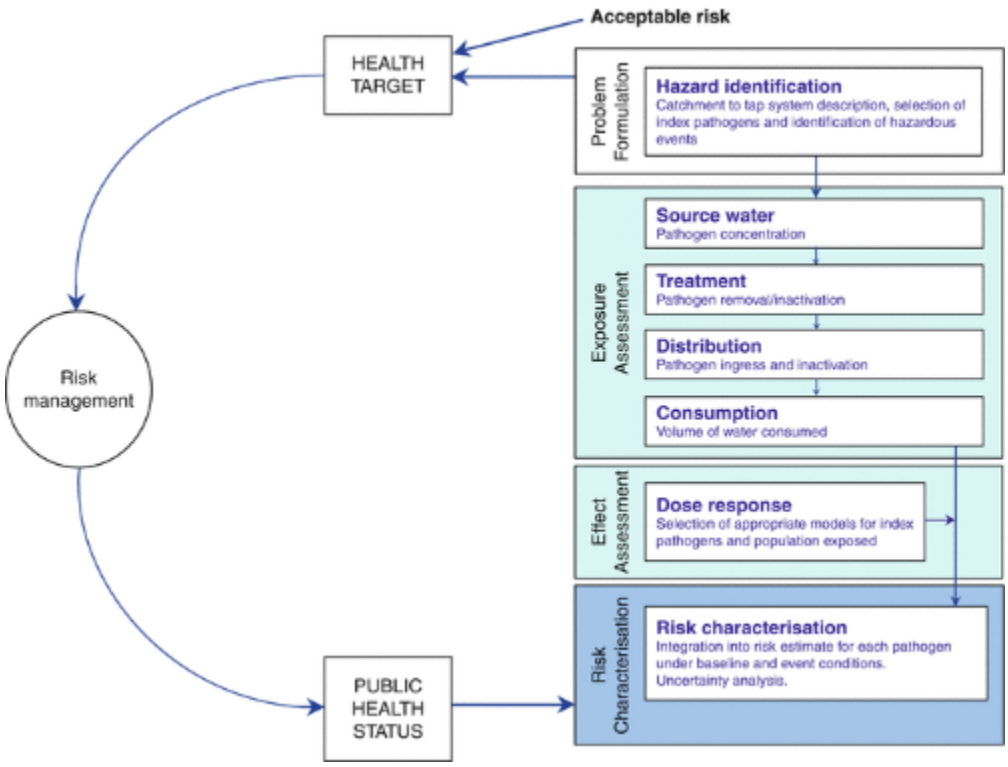
Risk assessment is used to answer the question: "Is my system able to produce and deliver drinking water that meets the health targets?" The risk assessment process requires quantitative information about the exposure of drinking water consumers to pathogens. This is provided by exposure assessment, one of the components of risk assessment. Quantitative information about pathogens in water sources, their removal by treatment and protection of the distribution network and drinking water consumption is collected and translated into an estimate of the exposure of consumers to pathogens through drinking water. To complete the risk assessment, the potential effect (the risk) of pathogen exposure is estimated through known dose-response models. As will be indicated later, the exposure assessment also provides valuable information to aid risk management in the prioritization of control measures.
An important question in risk management, especially in settings with an already high standard of drinking water safety, is "How far do we need to go with control measures?" This is an optimization that weighs the safety of the consumer against the costs of drinking water.
Quantitative microbial risk assessment (QMRA) can provide an objective and scientific basis for risk management decisions. Water utilities can use QMRA to assess whether they meet the health targets with their water treatment, storage, and distribution systems. This also provides the information to set the critical limits in the Water Safety Plans to ensure good performance. Good performance can now be based on a quantitative assessment of the contribution of the Critical Point (such as a disinfection or filtration process) to the overall safety, and limits can be set to ensure that the multiple barrier chain of water collection, treatment, and distribution as a whole does meet the target.
Risk assessment and risk management should not be regarded as two separate steps in the harmonized framework. To answer the question "Which control measures should be put in place to meet the target?" both the HACCP-based system and quantitative risk assessment provide valuable input: the hazardous events, the most important barriers in the system, the contribution of each of the barriers, target levels for control, the occurrence of weak elements in the chain, the quality of the available information, etc.

Quantitative Microbial Risk Assessment

Quantitative Microbial Risk Assessment (QMRA) is derived from the chemical risk assessment paradigm that encompasses four basic elements:

- A characterization of the problem, including the hazard
- Exposure assessment
- Effect assessment (dose-response)
- Risk characterization

Several QMRA frameworks have been published, such as the generic International Life Sciences Institute (ILSI) framework [8]. Here, most attention is given to exposure assessment and risk characterization of pathogens in drinking water. Therefore, the generic ILSI QMRA framework is expanded to highlight the elements that are important for exposure assessment and risk characterization in drinking water, and put in the overall WHO Safe Water Framework (Fig. 2).



Microbial Risk Assessment of Pathogens in Water. Figure 2 The steps of quantitative microbial risk assessment in the Safe Water Framework

Element 1. Problem Formulation and Hazard Identification

This is the initializing phase of QMRA to establish which specific questions need to be addressed. The scope and the boundaries of the QMRA process are determined in this phase. This requires communication between the risk managers (regulators, public health agencies, water utilities) and the risk assessors. The basic question to QMRA is: "Is my system able to meet the health targets?"
To conduct a QMRA, a good description of the system under evaluation is necessary and the hazards and hazardous events need to be identified.

Step 1. Description of the System from Source to Tap

The system for water treatment from catchment to tap is described, identifying the principal control elements and strategies.

Step 2. Hazard Identification

Hazard identification is the identification of the microorganisms within the system boundaries that cause human illness, the processes by which each microorganism causes illness and the type of illness(es) caused, and the identification of possible transmission routes and the significance of these routes [26]. QMRA is usually focused on a specific transmission route, in this example drinking water from a surface water source.
The ideal QMRA does not focus on a single pathogen only, but on a suite of "index pathogens" that cover the range of health risks and control challenges for the particular water supply system defined. Adequate control of these index pathogens implies that the health risk of other known pathogens is also adequately controlled by the system and that the system also offers protection against unknown pathogens.
Hazard identification consists of the following steps:
Description of the characteristics of the pathogens, especially those related to waterborne transmission (survival in water, resistance to treatment, etc.).

Description of what is known about the transmission routes of these pathogens and specifically what is known about waterborne transmission, the causes of waterborne outbreaks, and the relative significance of waterborne transmission compared to other routes.
Description of the illness (type, duration, incubation time, etc.) caused by the pathogens in the risk assessment, and available information about sequellae.
Description of what is known about protective immunity and secondary transmission.

Step 3. Description of Hazardous Events

In many cases, the majority of the risk is not determined during the normal (baseline) situation, but during hazardous events, such as rainfall leading to a high load of pathogens in source waters, or treatment failure or distribution network failure (or combinations thereof). It is therefore important to ensure that these hazardous events are incorporated in the QMRA, or that a separate QMRA is conducted to determine the (health) significance of the event.

Element 2. Exposure Assessment

Exposure assessment is the quantitative assessment of the probability that drinking water consumers ingest pathogens. A QMRA of drinking water usually requires the assessment of the levels of pathogens in source water and the changes to these levels by treatment, storage, and distribution, and finally the volume of water consumed.

Step 4. Assess Pathogen Occurrence in Source Water

Collect information about the occurrence of pathogens in source water . This is preferably based on a catchment survey, identifying the principal sources of contamination of the catchment and the conditions that may lead to peak events in source water, such as heavy rainfall or resuspension of sediments. Pathogen monitoring in source water can be carried out, using the information of the catchment survey, which needs to include assessment of peak events. The pathogen detection methods are ideally targeted to viable and infectious pathogens. The performance characteristics of the available detection methods for pathogens can have implications for the applicability of the data in risk assessment. These should be identified and evaluated in (the early stages of) the risk assessment process.

Step 5. Assess the Elimination of Pathogens During Treatment

Collect information about the removal or inactivation of pathogens during drinking water treatment processes. Ideally, data on removal of pathogens at full scale are used. In practice, however, several other sources of data have to be used to estimate pathogen removal, such as pathogen data of pilot or lab scale systems or data on model parameters (indicator bacteria, phages, spores, particles, etc.) on full, pilot, or lab scale.
The efficacy of treatment processes may vary, depending on feed water composition, operational control, temperature, etc. Moments or periods of poor or suboptimal performance are hazardous events and hence most significant for risk assessment.

Step 6. Assess the Changes in Water Quality During Storage and Distribution

Determine the likelihood of recontamination of stored and distributed water (e.g., by the E. coli monitoring of water in these reservoirs and pipes or loss of disinfectant residual) and the significance of these contamination events. In well-maintained piped supplies, recontamination events are rare and could be regarded as a result of a hazardous event (heavy rainfall, cross-connection, poor hygiene during repairs, etc.). In other piped and non-piped settings, recontamination events are common and may dominate the health risk.

Step 7. Consumption of Drinking Water

The other component of exposure assessment is the volume of water consumed by the population. Not only the average volume of water consumed is important, also the person-to-person variation in consumption behavior and especially consumption behavior of risk groups (in terms of sensitivity to infection or high level of consumption) is relevant. The available data suggest there is considerable difference between drinking water consumption within the population. This variation needs to be captured and incorporated in the risk assessment. Household treatment/point-of-use devices affect

the exposure. Hence, consumption data should be on consumption of drinking water without further treatment, such as heating or filters and include water that is drunk directly, but also cold tap water used for food preparation, ice, etc.

Step 8. Dose (Exposure) Estimation

Dose (or exposure) is the number of pathogens consumed per unit time. The information obtained in all steps of the exposure assessment needs to be combined into an estimate of the ingested dose. This is preferably a stochastic estimation, including the variability and uncertainty in all steps of the exposure assessment.

Element 3. Effect Assessment

The effect assessment is the determination of the health outcomes associated with the (level of) exposure to waterborne pathogens .

Step 9. Dose-Response Data

Dose-response characterizes the relation between dose magnitude, infectivity, and quantitative health effects to an exposed population. The microbial dose-response analysis records the incidence of a particular effect against dose of the agent. In most cases, this particular effect is infection, rather than symptoms of illness. For Cryptosporidium parvum for instance, there is a clear relation between ingested dose and the probability of infection, but not between dose and symptoms of intestinal illness.
Although the dataset is increasing, the number of dose-response studies with human volunteers is limited. Of most pathogens, only one or a few strains are tested in healthy adult volunteers. Information about strain-to-strain variability and the influence of the immune response of the hosts is still limited.
There are several dose-response models available and the type of model can have a very significant impact on the response that is attributed to exposure to low doses. The models and their limitations should be well understood when applying these in QMRA. Synergistic effects between pathogens are not incorporated in the current models.

Step 10. Host Characterization

For infectious diseases, the host susceptibility plays an important role in the health outcome of exposure. Exposure of persons with protective immunity will result in lower health outcomes than exposure of risk groups. During "Host Characterization" the characteristics of the potentially exposed populations that are suspected for susceptibility to a particular pathogen are evaluated.

Step 11. Health Outcome

Until now quantitative microbial risk assessment has been primarily focused on estimating the risk of infection. The relation between ingested dose and infection is relatively well defined, while the relation between dose and other health outcomes (illness, sequellae) is not available or less clear. This is one of the reasons why it is difficult to establish a direct relation between QMRA (on probability of infection) and epidemiological data (on symptoms of disease). The use of the risk (or probability) of infection is justified by the degree of conservatism in using infection as an endpoint and the inability to quantify the risk of more susceptible subpopulations [43].
However, waterborne diseases differ in nature, severity, and duration. A metric that takes into account the overall health burden of waterborne diseases is necessary. Ideally, this metric can also be used to describe the burden of the disease of chemical compounds, such as carcinogens, so all health risks can be weighed on the same scale.
In the new WHO guidelines for Drinking-Water Quality (GDWQ), the concept of Disability Adjusted Life Years (DALY) [31] is introduced as burden of disease metric in the drinking water guidelines.
The basic principle of the DALY approach is to weigh each health effect for its severity with (usually) death as the most severe outcome, multiply this weight with the duration of the health effect ("duration" of death being the remaining group life expectancy), and with the number of people in a population affected by the particular outcome. Summarizing all the health outcomes caused by a certain agent results in an estimate of the burden of disease attributable to this agent.
To be able to use DALYs in the QMRA, ideally the relation between exposure (dose) and different health outcomes is known. In the absence of sufficient data (which is usually the case), the dose-response relation for infection (as the first

step of the disease process) can be combined with data on the fraction of the exposed population falling ill from exposure (for instance, from attack rates in waterborne outbreaks) and data on the fraction of the ill population that contract more severe health outcomes (from health surveillance data).

Element 4. Risk Characterization

In the process of risk characterization, the information obtained in the exposure assessment and the effect assessment are integrated to obtain a risk estimate. This can be done as a point estimation: a point estimate of exposure can be entered into the dose-response relation to compute a point estimate of the risk of infection. The point estimate can be the "best" estimate, to obtain a measure of central tendency of the risk. In the case of computing various risk scenarios, the computed point estimates give a quantitative estimate of the consequences of the circumstances that produce a risk scenario.

An approach that allows the incorporation of the variability and uncertainty in the steps of the risk assessment chain is promoted by [23, 66]. This encompasses the characterization of the distribution of all data used for risk assessment and to combine these distributions into a distribution of the computed risk, for instance, by Monte Carlo analysis . This approach not only provides the risk manager with important information about the (un)certainty of the risk estimate, but also with the relative contribution of the uncertainty and variability in all steps of the risk assessment. It therefore guides the risk manager to the most appropriate options for efficiently minimizing the risk and the most significant research items to reduce the overall uncertainty of the risk estimate.

With high-level water supply , the baseline risk is usually very low. Under such conditions, hazardous events, such as peak contamination in the source water, treatment failure and especially the combination thereof and contamination events in the distribution network, are responsible for the majority of the risk. Most waterborne outbreaks have been traced to a combination of hazardous events [35] and it is likely that many events result in the presence of pathogens in tap water and hence the transmission of disease. Wherever possible, identify and evaluate these events separately in QMRA to understand the significance of these events. Analysis of events also brings forward opportunities for optimization of the system to prevent these events from occurring or reduce their impact on health.

Tiered Approach

Risk assessment is well suited for a tiered approach and this is also commonly used in risk assessment practice, both in human health risk assessment and in ecological risk assessment. The tiered approach allows an effective interaction between risk assessment and risk management, starting with a crude risk assessment, usually based on limited information to determine the urgency of the perceived problem, to prioritize the risk of different water supply sites or scenarios, and to determine the need of a more detailed study for a particular situation. This allows the effective allocation of resources to the sites or situations that give rise to the highest risk. There is no strict definition of the tiers, only that the initial QMRA is usually generic and simple and the specificity and complexity increase in subsequent tiers.

The most basic (but also most important) QMRA is a screening-level study. Starting with whatever information is available, a crude first evaluation is made. Usually, the available information is not specific to the system that is studied, but has to be extrapolated from the available scientific literature. So, in its simplest form, a QMRA can be performed with only a generic description of the water supply system.

The screening-level assessment may show that the risks are negligible, without much scientific doubt. In that case, the screening-level risk assessment can be used to demonstrate the safety of the system. Setting up a more detailed study is not warranted. Or the screening-level risk assessment may highlight that the risk is unacceptably high, again without much scientific doubt. Such a screening-level risk assessment is also very useful in comparing different scenarios for risk management, for example, different water treatment options.

If the outcome of the screening-level risk assessment is that there may be a health risk that is not negligible, there is an incentive for a next iteration of the risk assessment, the collection of site-specific data, for instance, on the presence of Cryptosporidium in the source water or catchment. The QMRA is repeated with the new, site-specific information. The options for the outcome of this second-level QMRA are the same as for the first iteration. In general, a result of any risk assessment is the identification of which information is missing and the prioritization of research needs [21].

The screening-level risk assessments usually work with point estimates of risk. The tendency is to use conservative or worst-case estimates, to "be on the safe side." But worst-case estimates, by nature, may overestimate the risk and it is not clear to the risk manager what the uncertainty of the calculated risk is, only that the uncertainty will be toward the

lower risk values (the nature of a worst-case assumption). More helpful for the risk manager is to provide a range of risks (interval estimate) that denote the variability and uncertainty in the risk estimate. In the case of the screening-level risk assessment, this can be achieved by using an average, worst, and best case, to illustrate the range of the risk that can be deduced from the available information and the level of certainty that is embedded in the QMRA.
Interval estimates require information about variability and uncertainty. Variability is the result of intrinsic heterogeneity in the input of the risk assessment, such as the variation in Cryptosporidium concentration in source water over time, or the variation in the removal of particles by a filtration process over time. Variability can be characterized if sufficient data points are collected. Uncertainty is the result of unknown errors in inputs of the risk assessment, such as errors in the measurement of Cryptosporidium or the assumption that certain indicator organisms can be used to describe the removal of Cryptosporidium by filtration. Uncertainty can be characterized by specific research activities, for example, to determine the recovery efficiency of the Cryptosporidium enumeration method or to compare the removal of Cryptosporidium to indicator organisms by filtration.
When sufficient data are available, a probabilistic risk assessment can be performed, where the input is described by statistical distribution functions to describe the confidence interval of the input itself and of the calculated risk.

Good QMRA Practice

Food safety has a longer history of employing microbial risk assessment to facilitate risk management. Several international bodies have produced guidance on good microbial risk assessment practice [13, 72]. The principles of good QMRA practice are also applicable to water safety. General principles are:

- Risk assessment should be clearly separated from risk management.
- Risk assessment should be soundly based on science.
- Risk assessment should be transparent: clear, understandable, and reproducible. It should follow a harmonized procedure based on the accepted standards of best practice.
- The scope and objectives of the risk assessment should be clearly defined and stated at the onset, in collaboration with the risk manager who is going to apply the results.
- The data used are evaluated to determine their quality and relevance to the assessment (taking into account their overall weight in the risk and uncertainty). If data are judged irrelevant or of too low quality, this should be justified. All data that are used are referenced.
- If data are variable, the variability should be documented and taken into account in the risk assessment, preferably in a probabilistic manner.
- All assumptions are documented and explained. Where alternative assumptions could have been made, they can be evaluated together with other uncertainties.
- The risk assessment should include a description of the uncertainties encountered in the risk assessment process. Their relative influence on the risk assessment outcome should be described, preferably in a quantitative (probabilistic) manner. Where point estimates are used for uncertain (or variable) quantities, the selected values should be justified and their influence on the assessment included in the uncertainty analysis.
- Conclusions should reflect the objectives and scope of the risk assessment, and include uncertainties and data gaps.

Uncertainty Analysis

Uncertainty is inherent in risk assessment [54]. Many (if not all) data have a degree of uncertainty. Sources of uncertainty in QMRA include:

- Extrapolation from dose-response data (though, unlike with toxic chemicals, many dose-response data are from human exposure)
- Limitations of pathogen detection methods
- Estimates of exposure

It is important to include the uncertainties in all steps of the risk characterization. The uncertainties in the estimates of exposure are usually dominant. Two approaches are used to determine how the uncertainty in the information in

individual steps of the risk assessment affect the uncertainty of the overall risk estimate: sensitivity analysis and Monte Carlo simulation. In sensitivity analysis, the value of each parameter in the risk assessment is varied, one at a time, along the uncertainty range of that parameter (e.g., Average and maximum concentration of a pathogen in water) to determine the effect on the final risk estimate. This procedure generates (1) the range of possible values of the final risk estimate and (2) the uncertainty in which of the parameters contribute most to the uncertainty of the final risk estimate. Sensitivity analysis is typically done in screening-level risk assessments. In probabilistic risk assessments, Monte Carlo simulation is the most widely applied method. Monte Carlo simulation needs a deterministic model for the risk assessment. The uncertainty (and variability) in each of the parameters in the risk assessment is expressed in a probability distribution. The simulation computes a final risk estimate by randomly selecting a value for each parameter in the model from the probability distribution for each parameter. This is repeated many (1,000-10,000) times, each time using a different set of random values from the probability functions. Monte Carlo simulation produces distributions of possible outcome values for the final risk estimate and the shape of the distribution identifies both the general tendency of the risk and the uncertainty of the risk estimate. Also here, the procedure gives information about the contribution of the uncertainty in individual parameters to the uncertainty in the overall risk estimate. While sensitivity analysis evaluates the impact of the uncertainty in each parameter separately and uses few values in the range of possible values of each parameter, Monte Carlo simulation evaluates the impact of the uncertainty in each parameter in combination with all other parameters and uses all possible values and the probability that they occur in the range of each parameter. Burmaster and Anderson [9] published principles of good practice for the use of Monte Carlo simulation in health risk assessments.

Applications of QMRA

The first quantitative microbial risk assessment studies on drinking water were conducted on viruses and Giardia [60]. Since the dose-response data from the first human volunteer study on Cryptosporidium [12] became available, several authors have performed QMRA for Cryptosporidium in water supply (Table 1). This makes the health risk of Cryptosporidium through drinking water the most intensively studied object in QMRA studies to date. The overview of QMRA studies for Cryptosporidium in water supply illustrates several issues:

Microbial Risk Assessment of Pathogens in Water. Table 1 QMRA studies on the risk of Cryptosporidium in public water supply

Authors	Exposure assessment	Effect assessment	Outcome	Type	Probability of infection average/95%-range
Medema et al. [47]	Cryptosporidium in source water, recovery data [39], viability data [39], removal of oocysts by full scale conventional treatment systems, [39], tap water consumption data [63]	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	3.6×10^{-5} [a] ($3.5 \times 10^{-7} - 1.8 \times 10^{-3}$)
Rose et al. [62]	Cryptosporidium in treated water [39]	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimates	5.0×10^{-2} ($4.4 \times 10^{-3} - 1$)
Rose et al. [62]	Cryptosporidium in ice prepared from tap water at the time of an outbreak, the latter corrected for the effect of freezing/thawing (90% loss of detectable oocysts) and for the recovery	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimates and comparison of observed and expected illness cases	-
Havelaar et al. [29]	Cryptosporidium in source water, recovery data, removal of anaerobic spores by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	1.3×10^{-4} [a] ($10^{-5} - 10^{-3}$)

Teunis et al. [66]	Cryptosporidium in source water, recovery data, viability data [39], removal of anaerobic spores by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	1.3×10^{-4} [a] ($4 \times 10^{-5} - 4 \times 10^{-4}$)
Teunis and Havelaar [68]	Cryptosporidium concentration in source water [5], recovery data [41], viable type morphology [39], removal by storage [66], removal of anaerobic spores by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection, illness and DALYs	Probabilistic	No treatment failure: 2.0×10^{-12} 95%: 2.8×10^{-10} Treatment failure: 1.5×10^{-8} 95%: 2.1×10^{-6}
Perz et al. [56]	Assumed concentration of Cryptosporidium in tap water, consumption of tap water [63], reduced by 40% for cold tap water consumption and by a further reduction of 33% for AIDS patients	Volunteer study with the Iowa strain [12], assumed threefold higher infectivity for AIDS patients	Probability of infection and illness (probability of illness 0.5 for general population and 1.0 for AIDS patients). Estimated reported cases in general and AIDS population	Point estimates, using two assumed concentrations of Cryptosporidium in tap water	$1.0 \times 10^{-3/-2}$ in general population $2.1 \times 10^{-3/-2}$ in AIDS population
Havelaar et al. [30] Gale [20]	Cryptosporidium in source water, recovery data, viability data [39], removal of anaerobic spores by conventional treatment, Hom model ozone inactivation [17], NL cold tap water consumption data. The exposure was compared to the exposure to bromate that was formed in the ozonation	Volunteer study with the Iowa strain [12]	DALY	Probabilistic, comparing Cryptosporidium to bromate burden of disease	1.0×10^{-3} [a] ($7.6 \times 10^{-4} - 1.5 \times 10^{-3}$)
Haas et al. [24] Haas [26]	Cryptosporidium concentration in ice manufactured from tap water during an outbreak, estimation of the inactivation by freezing and thawing, estimation of the duration of the contamination (on onset of cases), attack rate during the outbreak, tap water consumption data [63]	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimate, comparing expected and observed illness	1.1×10^{-2} [b]
Haas et al. [26]	Cryptosporidium concentration in distributed water during an outbreak, estimation of the duration of the contamination (on onset of cases), attack rate during the outbreak, assumed 1 L tap water consumption	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimate, comparing expected and observed illness	3.6×10^{-4} [b]
Gale [19, 20]	Cryptosporidium in source water [37] and removal of oocysts by full scale conventional treatment systems, [40], data on heterogeneity	Volunteer study with the Iowa strain, including immunity	Probability of infection		1.5×10^{-3} [b]
Haas and Eisenberg [27]	Cryptosporidium in different source watersheds, unfiltered system with chlorination, so removal/inactivation by treatment assumed as 0, tap water consumption data [63]	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimate and probabilistic	1.2×10^{-2} 1.2×10^{-3} ($1.2 \times 10^{-4} - 7.7 \times 10^{-2}$)

Medema et al. [48]	Cryptosporidium in source water, recovery data, removal of anaerobic spores by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimate	1.1×10^{-3} – 3.5×10^{-2}
	Cryptosporidium in source water, recovery data, removal of bacteriophages by soil passage and of Cryptosporidium in soil column studies, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Point estimate	0
	Cryptosporidium in source water, recovery data, viability and genotype data, removal of anaerobic spores by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	$<1.0 \times 10^{-4}$ with 91% certainty
Westrell et al. [70]	Cryptosporidium in source water, removal of particles by conventional treatment, inactivation by disinfection [18, 38], removal of oocysts by membrane filtration [2, 33]	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	Normal operation: 6.0×10^{-4} [a] (6×10^{-6}–4×10^{-2}) Filtration error: 4.0×10^{-5} [a] (6×10^{-7} –2×10^{-3})
	Cryptosporidium in sewage, reports of the water supply on treatment failure and contamination incidents in the distribution network	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	Reservoir contamination: 7×10^{-7} [a] (2×10^{-8}–2×10^{-6})
Masago et al. [46]	Cryptosporidium in source water [28], effect of rainfall, viability data [39], failure model for removal by conventional treatment, NL cold tap water consumption data	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	2.0×10^{-4} [a] (2.5×10^{-5} [c] – 2.5×10^{-3})
Gale [21]	Theoretical assumptions in scenario studies of treatment by-pass or failure	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	-
Pouillot et al. [59]	Assumed concentration in distributed water, recovery data, viability data (expert knowledge), French cold tap water consumption	Volunteer study with the Iowa strain for both infection and illness [12], immunodeficient mouse model [75]	Probability of infection and of illness for immunocompetent and immunodeficient persons	Probabilistic	At 2 oocysts/100 L: 1.8×10^{-2} 95%: 5.4×10^{-2}
Pouillot et al. [59]	Cryptosporidium in distributed water, recovery data, viability data (expert knowledge), French cold tap water consumption	Volunteer study with the Iowa strain for both infection and illness [12], immunodeficient mouse model [75]	Probability of infection and of illness for immunocompetent and immunodeficient persons	Probabilistic	2.1×10^{-2} 95%: 6.7×10^{-2}
Havelaar et al. [30]	Cryptosporidium in source water, recovery data, Cryptosporidium challenge study of conventional treatment	-	Quality score of exposure assessment factors	Uncertainty analysis	-

Haas et al. [25] JAWWA 88:131	Calculation of a Cryptosporidium concentration that corresponds with the 10^{-4} probability of infection (3.27×10^{-5}) oocysts L^{-1} (95% CI: 1.8−6.4 × 10)	Volunteer study with the Iowa strain [12]	Probability of infection	Probabilistic	(1×10^{-4})
Aboytes et al. [1]	Cryptosporidium in filtered drinking water, recovery data, infectivity data (cell-culture PCR)	Volunteer studies with the Iowa, UCP and TAMU with Bayesian data-analysis [51]	Probability of infection	Point estimate with confidence interval	8.2×10^{-3} 95%: 1.2×10^{-2}
EPA [15]	Cryptosporidium monitoring data (ICR and beyond), recovery data, infectivity fraction, treatment performance credits, USDA consumption data	Volunteer studies with Iowa, TAMU, UCP, using different models	Probability of infection, illness, death and cost	Probabilistic with sensitivity analysis	Scenario evaluation Pre-LT2 filtered: 8×10^{-5} ($<10^{-6}$ – 0.02); unfiltered 0.02 (0.002 to ~0.5)

[a]Median

[b]Average daily risk of infection during the outbreak

[c]Minimum annual risk

1. QMRA studies were conducted to:
    1. Evaluate the health risk of Cryptosporidium in specific water supply systems or water supply scenarios.
    2. Balance the health risk of Cryptosporidium in ozonated drinking water to the health risk of bromate formation by ozone [30]. For the assessment of exposure to Cryptosporidium, they used raw water monitoring data on Cryptosporidium, data on the removal of anaerobic spores by conventional treatment and an ozone disinfection model (the Hom model published by [17]) and a bromate formation model. The ingested dose of oocysts and bromate ions was translated to DALYs to allow comparison of the microbiological and chemical health risk. In their scenario, the health benefits of microorganism inactivation by ozonation outweighed the health losses by bromate formation.
    3. Demonstrate the need for additional treatment with UV [1]. They used monitoring data of Cryptosporidium in treated water, using a cell-culture-PCR technique to determine the concentration of infectious oocysts in treated water.
    4. Demonstrate the need for treatment optimization [46, 48].
    5. Illustrate the value of QMRA [47, 48, 59, 66, 68] and relation of QMRA to the Water Safety Plan [49, 65].
    6. Evaluate the risk of cryptosporidiosis in different water supply and sanitation scenarios [69].
    7. Evaluate the impact of failures in treatment and distribution on the health risk [70]. Failure reports were collected from operational logs/interviews. These failures were translated into an estimate of Cryptosporidium (and other pathogen) occurrence (which was the most uncertain step in this QMRA). They indicated that in this system, the health risk associated with normal operation was higher than from the very infrequent and short lasting reported incidents.
    8. Prioritize research needs [21], which illustrates how QMRA can be used to determine the relative significance of major, well-controlled and minor, less well-controlled routes of exposure and the impact of moments of reduced treatment performance.
    9. Perform a cost-benefit analysis of Cryptosporidium regulation that requires additional drinking water treatment for systems with relatively high levels of Cryptosporidium in source water [15].
2. Exposure assessment is in many studies hampered by incomplete "site-specific" data. The gaps in the site-specific data are filled by using data from the scientific literature. This is particularly true for the studies in the 1990s. As the use of QMRA progressed, more authors have collected site-specific information about most if not all steps in the exposure assessment.
3. Most studies used the dose-response data of the Iowa strain of C. parvum as published by DuPont and coworkers

[12]. Over the years, the dose-response relationships of more C. parvum strains have been published. One recent study on the risk of Cryptosporidium to fire fighters using recycled water used the dose-response data of the TAMU strain of C. parvum as this was the most infective strain [11]. Medema [50] present an approach for the use of a C. parvum dose-response relation, that combines the dose-response data that are published for four different isolates of C. parvum (Iowa, TAMU, UCP and Moredun).

4. The most frequently used health outcome is the probability of infection; a few studies also determined the probability of illness of the general population and the immunodeficient population [56, 59]. Two studies calculated the DALY resulting from the waterborne transmission of Cryptosporidium [67, 30].
5. Using the data of the Milwaukee outbreak [44], the calculated probability of infection/illness with QMRA was compared to the observed probability of illness in the outbreak as observed in the epidemiological investigations [24, 26]. The authors concluded that the results of QMRA and epidemiological investigation were consistent. The analysis of the exposure of the Milwaukee residents to Cryptosporidium via tap water was hampered by the lack of timely measurements of Cryptosporidium in the contaminated water. Unfortunately, this is the rule rather than the exception in waterborne outbreaks. The concentration had to be inferred from oocyst concentrations found in samples of ice that was prepared at the time of the water supply contamination and was corrected for the expected loss of detectable oocysts after freezing/thawing. The exposure assessment was therefore not very certain. In addition, the reported magnitude of the Milwaukee outbreak has been criticized by [36]. They claim that the background prevalence of gastrointestinal illness in the USA is much higher (1.2-1.4 episodes per person per year, or 0.10-0.12 per person per month) than the prevalence used by [44] (0.005 per person per month). Use of higher background prevalence would drastically reduce the estimated size of the Milwaukee outbreak.
6. The setup of the QMRAs sometimes used point estimates, but more generally a probabilistic approach is used to be able to estimate the level of uncertainty of the calculated probability of infection or illness.
7. Between the different studies, the calculated probability of infection can differ considerably see (Table 1). Within studies, the uncertainty of the risk estimate toward the higher health risk (illustrated by the difference between the average or median risk and the 95% confidence limit) is limited to around a factor of 10.

In general, it can be seen from these examples that QMRA has become an established tool to evaluate health risks of Cryptosporidium in (piped) drinking water supplies. QMRA requires input from data on exposure and dose-response and can be done in different levels of complexity. The next paragraphs give examples of the application of QMRA in water and illustrate the stepwise (tiered) approach that can be taken in QMRA and that QMRA can be conducted and be valuable in the absence of site-specific data and in developing countries.

QMRA to Assess the Safety of a Drinking Water Supply

Suppose that a water utility wants to evaluate if its surface water supply is at risk of significantly transmitting Cryptosporidium to its consumers, but has no specific information about Cryptosporidium in its source water or removal by its water treatment processes. A first exercise to get an idea of the level of risk could be a screening-level QMRA. The information on Cryptosporidium levels in source water can be derived from watershed use (see [50]), and for the water treatment processes default log-credits for the removal or inactivation of Cryptosporidium are available [49]. For instance, if the water supply system uses a watershed that can be characterized as moderately polluted and treats this source water with off-stream storage reservoirs and a conventional (coagulation/filtration/chlorination) water treatment system, using the scientific database, the expected concentration of Cryptosporidium in source water can be estimated at 0.1/L and the removal by the subsequent water treatment processes can be estimated at 0.5 + 2.5 = 3.0 logs removal. Hence, the estimated concentration of Cryptosporidium in drinking water is 1×10^{-4}/L. With a conservative best estimate of consumption of cold tap water of 0.78 L/day (3.49 glasses of 0.25 L, [53]), the average probability of exposure to Cryptosporidium is 8.7×10^{-5} per person per day. With the combined dose-response relation of the four C. parvum strains, the probability of infection is estimated at 3.8×10^{-5} per person per day, which amounts to 1.4×10^{-2} (=1.4%) per person per year. This is a first estimate of the health risk related to Cryptosporidium in this specific water supply system. Similarly, such an exercise can be used to evaluate different scenarios of risk management to reduce this risk (if required) such as measures to improve the catchment or install additional treatment processes. An example of a practical application of such a screening-level risk assessment is given in Medema [50], where a large water supply company uses the screening-level QMRA to prioritize risk management of its water supply systems.

Comparing Water Supply Scenarios with QMRA

Piped and non-piped water supply in Uganda [34].

In Kampala, 72% of the population uses piped water supplies. 20% of the population uses piped water through household connections; the rest collects water at standpipes and stores it in-house. The piped water is produced from Lake Victoria water through (coagulation/settling) rapid sand filtration followed by chlorination. The rest of the population (28%) uses protected springs for their water supply.

Data on thermotolerant coliforms were available from Lake Victoria and from the protected springs and the household containers. Using an estimate of the percentage of E. coli within the thermotolerant coliforms and an estimate of the percentage of pathogenic E. coli within E. coli, the thermotolerant coliform concentration data were translated to pathogenic E. coli concentrations. For the removal of (pathogenic) E. coli by the water treatment processes, the authors used a 3-log credit for the physical removal processes and an additional 2-log credit for the chlorination. This was used to calculate the concentration of pathogenic E. coli in drinking water. With data or estimates on consumption of unheated drinking water, dose-response for infection, probability of illness when infected, and disease burden (DALY), the concentration of pathogenic E. coli in drinking water was translated into the estimated disease burden by exposure (Table 2).

Microbial Risk Assessment of Pathogens in Water. Table 2 Assessment of disease burden for pathogenic E. coli from different water types (adapted from [34])

	Piped water following treatment	Piped water in distribution	Household storage water	Protected spring water
Raw water quality thermotolerant coliforms/L	150		30	140
Raw water quality E. coli/L	143		28.5	133
Raw water pathogenic E. coli/L	11.5		2.3	10.6
Treatment effect (log)	5		0	0
Drinking water quality (/L)	1.15×10^{-4}	0.18	2.3	10.6
Consumption of unheated drinking water (L)	1			
Exposure (pathogens/day)	1.15×10^{-4}	0.18	2.3	1.06×10^{1}
Dose-response parameter (exponential)	0.001			
Risk of infection (day)	1.15×10^{-7}	1.80×10^{-4}	2.30×10^{-3}	1.06×10^{-2}
Risk of infection (year)	4.20×10^{-5}	6.57×10^{-2}	8.40×10^{-1}	3.87×10^{0}
Risk of diarrheal disease given infection	0.25			
Risk of diarrheal disease	1.05×10^{-5}	1.64×10^{-2}	2.10×10^{-1}	9.67×10^{-1}
Exposed fraction	0.31	0.1	0.42	0.28
Disease burden (DALYs)	1.04×10^{-6}	5.26×10^{-4}	2.82×10^{-2}	8.67×10^{-2}

Similar assessments were made for Cryptosporidium and Rotavirus exposure for the population using piped water supply. For Cryptosporidium, they showed that treatment failure would result in a very significant increase of the disease burden (from 10^{-4} to 4 DALYs per person per year). The authors have compared the calculated levels of disease burden to the WHO reference level of risk (10^{-6} DALY). Upgrading the treatment would be necessary to achieve this health target, but the authors argue that, given the low level of access to piped water in the home and the disease burden associated with the use of alternative (more contaminated) sources, this would not be cost effective. Improving access to piped water supply in homes, sanitation and hygiene would be more effective in reducing the disease burden.

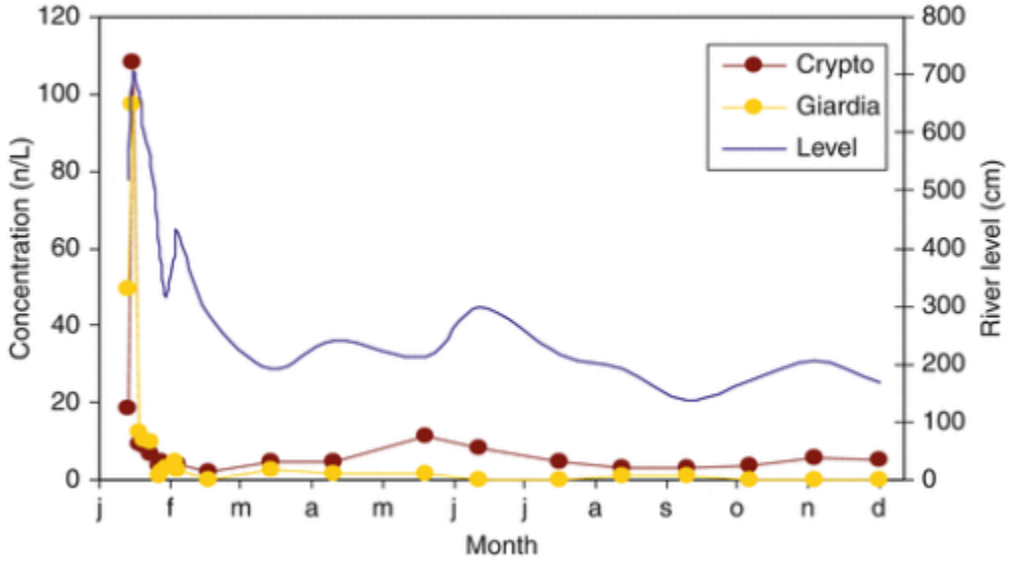
This example illustrates that QMRA is feasible also in settings with limited data. The authors discuss limitations and assumptions used in their study, but illustrate the value of system assessment to inform risk management of the area

where control measures will be most effective.

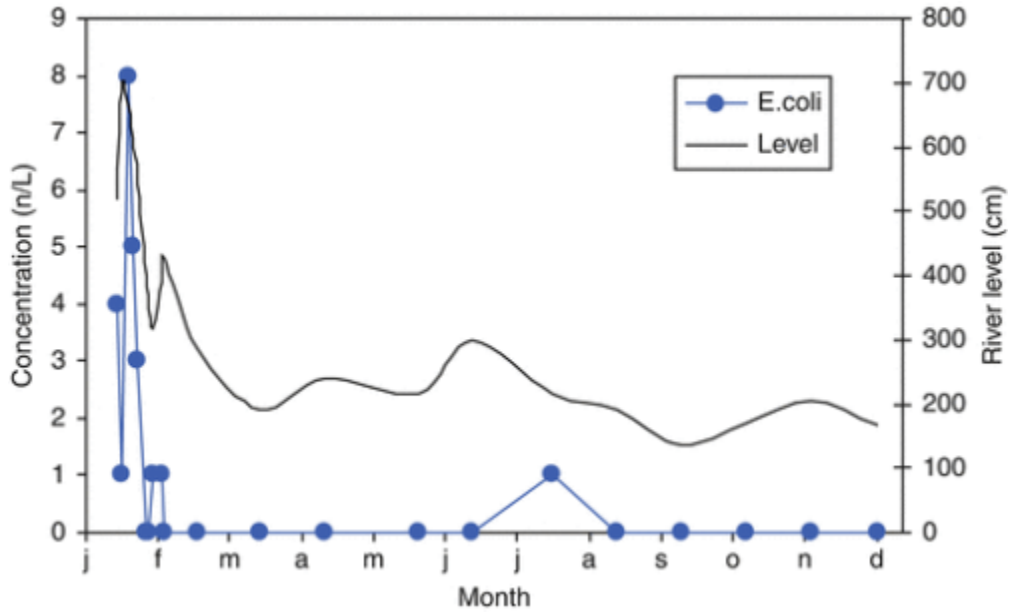
QMRA to Evaluate the Health Risk of Hazardous Events health risk

Many outbreaks of intestinal illness caused by consumption of contaminated drinking water in affluent nations have been associated with hazardous events, such as heavy rainfall (both for surface and groundwater systems), failures in a treatment process, failures in the integrity of the infrastructure (wells, distribution network), cross-connections in the distribution network, etc. For an overview, see [35]. Additional hazardous events can be identified for non-piped supplies, especially contamination of the water in storage containers. Also, events that lead to a stop in supply of drinking water (due to power or treatment failure, or indeed absence of sufficient quantities of source water) are hazardous events in themselves, since water is essential for life and hygiene.

Water quality testing can help to identify peak events. Often, peak events can be indicated by simple parameters, such as rainfall, river flow, turbidity, etc., and hence their detection does not require advanced equipment or expertise. It does require knowledge of the water supply system, including its catchment. In Microrisk, a European study on microbial risk assessment of drinking water , information was needed about pathogen occurrence in source (surface) water of the water supply systems under study [49]. Knowing the potential importance of peak events, catchment surveys were conducted to identify contamination sources and to identify events that could lead to peak pathogen contamination of the source water. One system used bank filtration and subsequent treatment to produce drinking water from a large river. Historical (50 years) data on the water level of the river showed that an increase of ≥3 m within 5 days occurred 1.1% of the time (3.9 days per year on average). This river level rise was used as a criterion to trigger peak event sampling. A dry weather flow sampling scheme was also in place, with monthly pathogen samples. During monitoring, one peak event was encountered and peak event samples were taken, showing a sharp increase in the concentration of Cryptosporidium and Giardia concentration in the river (Fig. 3). Event samples were also taken from the bank filtrate. The E. coli were detected in the bank filtrate only at the time of the peak event (Fig. 4).



Microbial Risk Assessment of Pathogens in Water. Figure 3 Cryptosporidium and Giardia in river water during a peak event (Data from [49])



Microbial Risk Assessment of Pathogens in Water. Figure 4 E. coli breakthrough of bank filtration during a peak event in the river see (Fig. 3, data from [49])

Similarly hazardous events may occur in water treatment (i.e., disinfection failure) or distribution (cross-connection, ingress during main breaks, no pressure period or repair). A QMRA to determine the health effect of ingress of fecal contamination in municipal piped distribution networks is given in [42]. In the Microrisk project, the health risk associated with several source and treatment hazardous event scenarios in the different water supply systems (called Catchment-to-Tap Systems or CTS) studied was determined and compared to the baseline health risk in these systems in a Monte Carlo simulation [64].

Hazardous events were identified in discussions with local water suppliers and from SCADA data. Of these, five were selected and evaluated with QMRA (Table 3).

Microbial Risk Assessment of Pathogens in Water. Table 3 Hazardous event impacts on risk

CTS	Pathogen	Hazardous event	Total duration of event	Baseline risk	Baseline + hazardous event risk
				(person^{-1} year^{-1})	
1	Cryptosporidium	Loss of filtration due to petroleum spill necessitating cleanup. Only remaining treatment is chlorination	7 days	1.4×10^{-5}	1.7×10^{-2}
5	Norovirus	No intake closures leading to periodic high concentration of virus in source water	57 days	$<5.8 \times 10^{-4}$	2.7×10^{-2}
		Delay in intake closure of 4 h for each of 29 events of high virus concentration in source water per year	4.75 days		3.4×10^{-3}
6	Campylobacter	Loss of disinfection capacity: total suboptimal chlorination periods based on analysis of SCADA data - worst case of total loss of disinfection assumed	1.5 h	2.5×10^{-6}	3.2×10^{-6}
8	Campylobacter	Short-circuiting leads to reduced (1 log) removal in storage reservoir for 24 h. Nine short-circuiting events occur per year	9 days	1.7×10^{-5}	3.4×10^{-5}
		Short-circuiting leads to reduced (1 log) removal in storage reservoir for 24 h. Nine short-circuiting events occur per year. During one of these periods chlorination loss occurs due to power failure for 2.4 h (0.1 days)	0.1 days		1.8×10^{-4}

The risk estimates in brackets are based on upper 95th percentile uncertainty and are derived from upper limit inputs rather than typical source water concentrations

In the case of the CTS 1 (a surface water supply) the local managers were concerned about the prospect of a motorway fuel spill and its potential impact on the treatment plant. It was speculated that even small quantities could foul major filters (Rapid Sand Filter and Granular Activated Carbon filters) and reactors (ozone contact tanks) and necessitate cleaning. This led us to simulate a cleanup period of 7 days during which protection was provided by chlorination alone and hence the system was vulnerable to Cryptosporidium contamination because of its resistance to chlorine.
It can be seen that the annual risk of infection by Cryptosporidium rises by a factor of 1,000 and the estimated probability of infection is much higher than 10^{-4} per person per year. Further, even if the repair period could be reduced to 1-2 days, the additional risk would still be great and hence other action such as a boiled water alert on top of chlorination would need to be considered.
CTS 5 is a surface water supply system with the option to close water intake. If no intake management were in place the average annual risk would have been at least 19 times higher. The impact of a delay in closing the intake was also substantial. This highlighted the need for timely warning of event onset where source extraction is being managed.
CTS 6 included extensive diary and SCADA (Supervisory Control and Data Acquisition) data detailing performance of the chlorination. This information allowed determination whether chlorination failure was occurring. Analysis of the in-line chlorine monitoring data indicated that at worst chlorine dosing failed for a total time of 1.5 h over a 12-month period. The impact of simulated worst-case failure on Campylobacter showed a detectable but only small increase in health risk.
The final scenario considered was that of multiple concurrent hazardous events. A concern for CTS 8 and CTS 6 type systems, which draw their supply from a reservoir, is that during high run-off events there can be concurrent polluted input and short-circuiting [32]. Further, storms frequently cause power failures, which could affect treatment plant equipment such as dosing pumps. Two scenarios were considered with these events in mind. Concurrent contamination of runoff and short-circuiting of the reservoirs were estimated to double health risk for Campylobacter . With the combination of a short duration power failure leading to chlorination loss during a storm could increase annualized risk 11-fold in a short time, confirming the need for avoiding or actively managing periods of concurrent hazardous events.
The value of the hazardous event analyses illustrated lies not only in the actual estimates presented. They also demonstrate how QMRA can be used to evaluate events and other hazardous scenarios to produce risk estimates useful for management. In the case of CTS 1, it was clear that filtration shut down even for a short period posed high risks because of the contamination levels in the source water. Selective water intake at CTS 5 is a beneficial management activity. At CTS 6, chlorine dosing was shown to be maintained at a level sufficient to reduce risks arising from plant failure. The CTS 8 analysis showed that baseline operating conditions provide sufficient barrier protection to mitigate a run-off and short-circuiting event, but with a concurrent event (chlorination failure) pose a significant threat.

QMRA for Water Reuse

In (semi) arid conditions, there is (increasing) water scarcity and competition between agriculture and urban uses of this scarce resource. Wastewater is in most cases a reliable (in terms of quantity) source of water and valuable source of nutrients for agriculture. Wastewater reuse in agriculture is a form of water and nutrient recycling that is practiced worldwide, especially in arid and semi-arid areas. Also the (re)use of gray water in urban areas for applications such as toilet flushing in homes, gardening, etc., is becoming more common.
The new WHO Guidelines for safe use of wastewater, excreta, and gray water are based on the Safe Water Framework (Fig. 1). QMRA is presented in these WHO guidelines as useful tool to estimate the health risks associated with wastewater reuse in different scenarios and for different pathogens. The guidelines contain several references to the application of QMRA in wastewater reuse . In the next paragraphs, three examples of the use of QMRA in water reuse are given.

Comparing Risks Between Different Uses of Reclaimed Wastewater (California)

The first QMRA to estimate the disease risk associated with the reuse of (treated) wastewater was [3]. They evaluated the risk of an infection with enteric viruses (Poliovirus 1 and 3 and Echovirus 12) when chlorinated or unchlorinated tertiary effluent was used for:

- Irrigation of a golf course
  The exposure scenario was a golf course with night time irrigation with tertiary treated wastewater effluent and person golfing twice a week. Each day this person would be exposed to 1 mL of reclaimed water during handling

and cleaning of golf balls. The pathogen concentration in this reclaimed water was calculated from data on enteric viruses in chlorinated and unchlorinated effluent and virus decay on the golf field.

- Spray irrigation of food crops
  After spray irrigation, it was assumed that 10 mL of reclaimed water was left on each portion of crops eaten raw. The spray irrigation was stopped 14 days before harvesting and the virus die-off due to desiccation and sunlight exposure was included in the calculation.
- Swimming in recreational water
  This recreational water was assumed to be an impoundment that was, during summer, completely made up out of reclaimed water. No dilution or die-off was assumed. A swimmer was assumed to ingest 100 mL each swimming day and to swim 40 days in a year.
- Groundwater recharge near domestic wells
  This exposure scenario was based on the proposed Californian groundwater recharge regulations. The nearest domestic well was assumed to receive 50% reclaimed water that had been passing through 3 m of unsaturated soil beneath the recharge basin during a period of 6 months. The people drinking from this well were assumed to consume 2 L/day.

The input data were:

- Concentration of culturable enteric viruses in unchlorinated secondary effluent: 5−734/L (90% and maximum, respectively)
- Concentration of culturable enteric viruses in chlorinated tertiary effluent: 0.01-1.1/L
- Removal of enteric viruses by full tertiary treatment (flocculation, clarification, filtration, chlorination): 5 logs
- Virus decay rate: 0.69/day (first order die-off kinetics)
- Fraction of virus remaining after percolation through the unsaturated soil $c/c_0 = 10^{-0.007\ L}$, where L is the depth of the unsaturated zone in centimeters
- Dose-response parameters for echovirus 12 and poliovirus 1 and 3

The concentration of viruses in reclaimed water was taken from data from surveys of secondary and tertiary effluent. They calculated the exposure to the viruses in the different exposure scenarios. Annual risks were calculated from the maximum concentration found in chlorinated tertiary effluent (1.1 culturable virus unit L^{-1}) and exposure in the different applications (Table 4).

Microbial Risk Assessment of Pathogens in Water. Table 4 Annual risk of exposure to viruses for different applications of reclaimed water

Exposure scenario	Echovirus 12	Poliovirus 1	Poliovirus 3
Irrigation of golf course	1.0×10^{-3}	3.5 E-5	2.5 E-2
Spray irrigation food crops	4.5×10^{-6}	1.5 E-7	1.1 E-4
Recreational impoundment	7.4×10^{-2}	2.6 E-3	8.4 E-1
Groundwater recharge	5.9×10^{-8}	5.4 E-9	2.3 E-8

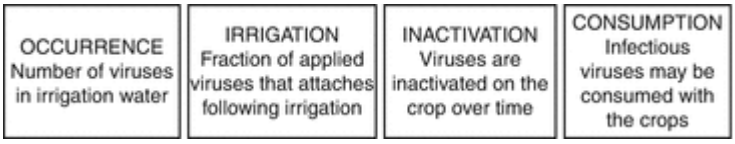
This QMRA showed that the virus risk was highest when reclaimed wastewater was used in recreational impoundments and golf course irrigation. This maximum concentration was found in only 0.1% of the samples (with 99% of the samples with virus concentrations below the detection limit), so they also calculated the risk with a virus concentration of 1/100 L, which were approximately 100-fold (2 logs) lower.

The value of the QMRA was that it provided a comparative basis for addressing the treatment and fate of enteric viruses in wastewater reuse and showed that the risk can further be mitigated by controlling exposure to reclaimed water.

Health Risk of Reuse for Crop Irrigation (Australia; Probabilistic)

In the previous example, the available data and assumptions were used to generate point estimates. This example shows how the variability in available data can be used to determine the uncertainty that is associated with each of the components in a QMRA.

The use of wastewater for irrigation of food crops that are eaten raw is common practice in many arid and semi-arid regions [57] constructed a QMRA-model for evaluating the risks associated with the consumption of wastewater irrigated lettuce crops. The exposure assessment in this model consisted of four process steps:



Exposure to viruses was calculated as:

$$\text{Exposure} = N \times f \times S(t) \times q$$

where

- N is the number of viruses in the irrigation water applied to the crop
- f is the fraction of those viruses that survive the irrigation process and attach to the lettuce plant
- S(t) is the fraction of viruses remaining infectious at consumption
- q is the quantity of crop consumed

For each step a best estimate and an extreme estimate were selected (Table 5). This allowed analysis of the sensitivity of the QMRA to each of the model parameters.

Microbial Risk Assessment of Pathogens in Water. Table 5 Best and extreme estimates for parameters of exposure to viruses in wastewater reused for irrigation of lettuce

Model component	"Best" estimate	"Extreme" estimate
Virus occurrence	2.6 (virus units L^{-1})	470,000 (virus units L^{-1})
Virus attachment (f)	0.024	0.071
Virus inactivation: S(t)	h1 = 2.5 day^{-1}	h1 = 2.0 day^{-1}
Bi-phasic inactivation	h2 = 0.5 day^{-1}	h2 = 0.3 day^{-1}
$Ct = aC_0 * h1 + (1 - a)C_0h2$	a = 0.12%	a = 0.96%
Consumption per event q	100 g	300 g

Sources: Californian dataset used by [3, 76]. All other data were derived from [57, 58].

The authors calculated the Factor Sensitivity (FS = log ($N_{extreme}/N_{best}$), with N being the number of viruses in the extreme or best estimate) for each of the components. Already obvious from the table above is the high impact of the estimate for the virus concentration in wastewater (FS = 5.49). Less obvious from the table is the high impact of the estimate of virus inactivation (FS = 2.2). This is of course time dependent; the authors used 14 days as the time between final irrigation and consumption. A shorter interval reduces the impact of virus inactivation, since the inactivation is less. The uncertainty associated with virus attachment (FS = 0.45) and consumption (FS = 0.48) was considerably less.

This simple mathematical approach yielded not only the risk estimates associated with wastewater reuse for food crop irrigation, but also the (un)certainty associated with each of the components in the exposure of crop consumers to viruses that remain on the crops at the time of consumption.

Guidelines for Safe Reuse (Australia)

QMRA can be used to estimate health risks from exposure to pathogens via wastewater reuse in agriculture , as illustrated in the above examples. In the National guidelines for water recycling in [6], QMRA is used for a different purpose: to calculate health-based performance targets for recycled water systems. In these guidelines, the Australians use a health-based target as a benchmark for safety that has to be met by each water reuse system. They use the health-based target that WHO has defined in their GDWQ: 10^{-6} disability adjusted life years per year (DALY, see Box 1 for more information about this disease burden metric) as their tolerable level of risk.

This health-based target is translated to performance targets for the reuse system with respect to microbial hazards. The concentration of pathogens in the source water for the reuse system (raw/treated sewage, gray water, etc.) and the level

of exposure of people to the recycled water (via crops, aerosols, ingestion) determine how much reduction of pathogen exposure is required to meet the 10^{-6} DALY/year target.
In formula:

$$PT = \log(C \times E \times N / DALYd)$$

in which

- PT is the performance target (required log reduction)
- C is the concentration of pathogens in source water (in these guidelines: 95th percentile of concentration data)
- E is the exposure (volume (L))
- N is the average frequency of exposure (number/person/year)
- DALYd is the pathogen dose that is equivalent to a DALY of 10^{-6} per year, a translation of the 10^{-6} DALY target to a pathogen dose target, taking into account the pathogen's dose-response relation and the fraction of persons that contract illness when infected.

Since sewage and gray water may contain a wide range of pathogens and it is not feasible to do this QMRA for all, it is more practical to select reference pathogens, pathogens that represent a major group of pathogens. The philosophy is that when risk management is aimed at these reference pathogens, the other pathogens from these groups will also be adequately controlled. For protozoa and helminth eggs, Cryptosporidium is selected as reference pathogen because it is reasonably infective and more difficult to control by chlorination and filtration than other protozoa or helminth eggs (DALYd is 1.6×10^{-2}, 95th percentile in sewage: 2,000/L). For bacteria, Campylobacter is selected because of its infectivity and high prevalence (DALYd is 3.7×10^{-2}, 95th percentile in sewage: 7,000/L). For viruses, rotavirus is selected because of its high infectivity and the availability of dose-response data. Since no data on rotavirus in sewage were available, but data on adenoviruses occurrence were available, these latter data are used and combined with the rotavirus dose-response data (DALYd is 2.5×10^{-3}, 95th percentile in sewage: 8,000/L).
So with concentration C in source water as known and the DALYd as a constant per reference pathogen, the level and frequency of exposure are needed to determine the performance target for the reuse system.
For a range of intended uses of recycled water the associated level and frequency of exposure was (point) estimated from available scientific and statistic data. For example, for exposure by consumption of commercial food crops irrigated with recycled water the level of exposure was estimated at 5 mL for a service of lettuce and 1 mL for a service of other raw produce, with an annual frequency of 70 and 140 services, respectively. Similar exposure estimates were determined for garden irrigation, municipal irrigation, fire fighting, toilet flushing, washing machine use, and cross-connections.
Now the performance target for the use of recycled wastewater for commercial crop irrigation can be calculated:
Exposure for lettuce is 0.005 × 70, for other raw produce 0.001 × 140; this totals to 0.49 L/year

$$\begin{aligned} \mathrm{PT}_{\mathrm{Cryptosporidium}} &= 2,000 \times 0.49 / \left(1.6 \times 10^{-2}\right) \\ &= 4.8 \ \log \\ \mathrm{PT}_{\mathrm{Campylobacter}} &= 7,000 \times 0.49 / \left(3.7 \times 10^{-2}\right) \\ &= 5.0 \ \log \\ \mathrm{PT}_{\mathrm{Rotavirus}} &= 8,000 \times 0.49 / \left(2.5 \times 10^{-3}\right) \\ &= 6.1 \ \log \end{aligned}$$

There are different ways to manage the risk associated with water recycling: prevent pathogens from entering recycled water, remove pathogens from recycled water by treatment processes, and reduce exposure by using restrictions or preventive on-site measures: restricted access, withholding periods before harvesting, controlled application (drip or subsurface irrigation). The Australian guidelines have assigned default performance credits to a range of treatment processes and on-site preventive measures and give examples of how the combination of these two types of risk management options can be used to achieve safe water recycling.

Box 1. DALY

Disability Adjusted Life Years (DALYs) is as a metric for translating the risk of disease burden a general health burden per case of illness. The DALY accounts for the years lived with a disability (YLD) plus the years of life lost (YLL) due to the hazard (compared to the average expected age of death in a community). One DALY per million people a year roughly equates to one cancer death per 100,000 in a 70-year lifetime [73]. The DALY is calculated as the product of the probability of each illness outcome with a severity factor and the duration (years). Calculation of the DALY contribution per infection is undertaken using:

$$\mathrm{DALY} = \sum_{i=1}^{n} P(\mathrm{ill}|\,\mathrm{inf}) \times P(\mathrm{outcome}_i|\mathrm{ill}) \times \mathrm{Duration}_i \times \mathrm{Severity}_i$$

where n is the total number of outcomes considered
P(ill|inf) is the probability of illness given infection
P(outcome|ill) is the probability of outcome i given illness
Duration $_i$ is the duration (years) of outcome i
Severity $_i$ is the severity weighting for outcome i.

The advantage of using DALYs over an infection risk end point is that it not only reflects the effects of acute end points (e.g., diarrheal illness) but also the likelihood and severity of more serious disease outcomes (e.g., Guillain-Barré syndrome associated with Campylobacter). Disease burden per case varies widely, but can be focused on a locality. For example, the disease burden per 1,000 cases of rotavirus diarrhea is 480 DALYs in low-income regions, where child mortality frequently occurs. However, it is only 14 DALYs per 1,000 cases in high-income regions, where hospital facilities are accessible to the great majority of the population. Disease burden estimates for different drinking water contaminants is summarized in Table B1.

Microbial Risk Assessment of Pathogens in Water. Table B1 Summary of disease burden estimates for different drinking water contaminants

	Disease burden per 1,000 cases		
	YLD	YLL	DALY
Cryptosporidium parvum	1.34	0.13	1.47
Campylobacter spp	3.2	1.4	4.6
STEC O157	13.8	40.9	54.7
Rotavirus			
High-income countries	2.0	12	14
Low-income countries	2.2	480	482
Hepatitis-A virus			
High-income countries, 15-49 years	5	250	255
Low-income countries	3	74	77

Source: Reproduced from [31].

Future Directions

The examples given in the previous paragraphs illustrate how QMRA can be applied to assess microbial health risks associated with systems where people may be exposed to pathogens through the use of water. QMRA is used to evaluate individual systems (against health-based targets), compare different systems or scenarios and to evaluate the significance of hazardous events and system failures in municipal piped water supply , but also non-piped water supply, and for wastewater and gray water reuse. Others have also demonstrated the use in recreational waters [4].
Risk assessment also allows comparison of the effort and resources put into the provision of safe water systems and

resources allocated to manage other health risks. However, given the current state of the art and especially the lack of available quantitative data, QMRA has to rely partly on assumptions. Given the current level of uncertainty in quantitative risk assessments of water systems, the outcome should be regarded as an indication of the level of safety, rather than an absolute assessment of health risk. The outcome can be used to guide the risk management direction to pathogen control and to select the most appropriate control measures.
The benefit of risk assessment is that it gives a better understanding/breakdown of the problems and of important data. Additionally, the risk concept allows us to focus and prioritize research on the areas where important pieces of information are missing.

Improving the Technique of QMRA

The science of risk assessment is increasingly complex; most of the current QMRA work uses the probability of infection as end point. Infection is the first step in the disease process, but does not reflect the severity of the disease, including potential serious health effects that may arise in a particular subpopulation. Some studies have been using burden-of-disease and cost-of-illness measures [45]. This improves the assessment of the magnitude of the adverse effect of pathogens exposure via water and allows balancing pathogen risks with other risks. The dynamics of infectious diseases with secondary transmission and the effect of immunity and sensitive subpopulations have been largely neglected. Several studies are exploring ways to incorporate these disease dynamics into account [14].
The large variability of pathogens in water and the limited availability of data (especially in relation to peak events) and the variability in treatment efficacy are very important issues to take into consideration in QMRA. More data need to be collected, and monitoring programs of water suppliers should be targeted more toward the provision of information for QMRA. Pathogens to be selected for QMRA should be detectable in the water systems with reliable analytical techniques. The use of reference pathogens, pathogens that are critical for the control measures taken in water supply, is recommended. The variability and limited data available will cause uncertainty in the risk assessment, but compared to chemical risk assessment with large uncertainty factors, this is not inhibitive for the implementation of microbial risk assessment.

Improving the Utility of QMRA

QMRA can be done at different levels of sophistication. Sophisticated QMRA can take considerable amounts of time and resources. The level of detail in the QMRA and the extent of the uncertainty analysis that is needed to address a particular problem has to be appropriate only to the extent that is needed to help risk managers decide. QMRA lends itself well for a tiered approach, where the sophistication increases only if the risk manager requires better information to make a decision.
The National Research Council in the USA has advised USEPA to adopt a framework for risk-based decision making to make risk assessments more useful for risk management decisions [55]. In this framework, improved stakeholder involvement should also help to improve the acceptance and utility of risk assessment.
QMRA is a process that requires input from several disciplines. Researchers that are trained in a specific discipline have to learn to combine their data and knowledge with data and knowledge from other disciplines in a (probabilistic) risk assessment framework. And risk assessment is being extended to address broader questions in environment and health: risk-risk trade-offs and cost-benefit analysis. Development of guidance and training on QMRA is needed to strengthen the capacity of QMRA researchers.
Assessing the microbial risks of water systems is a relatively young field of science. It has the capacity to further professionalize safety management in water by providing science-based, objective, credible and proportionate information to help risk managers make informed decisions.

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pp 437-488

Microbial Risk Assessment of Pathogens in Water

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DOI: 10.1007/SpringerReference_226419

URL: http://www.springerreference.com/index/chapterdbid/226419

Part of: Encyclopedia of Sustainability Science and Technology

Editor: Dr. Robert A. Meyers

PDF created on: February, 27, 2013 19:05