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International Environmental Modelling and Software Society (iEMSs)
7th Intl. Congress on Env. Modelling and Software, San Diego, CA, USA,
Daniel P. Ames, Nigel W.T. Quinn and Andrea E. Rizzoli (Eds.)
http://www.iemss.org/society/index.php/iemss-2014-proceedings

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Abstract: Intelligent risk-based decision-making requires a clear and transparent framework, and as part of that framework, includes a tractable analysis and balancing of various qualities of information from numerous sources. The purpose of this paper is to provide a number of examples on the application of QMRA, and how the information was utilized to aid and facilitate decision-making as part of the regulatory process for evaluating water recycling and municipal treatment plant discharges.

Keywords: Risk assessment; pathogens; mathematical modeling; waterborne disease; environmental policy

1. INTRODUCTION

Risk analysis is an integral part of the weight-of-evidence process in aiding regulatory decision-making. Intelligent risk-based decision-making requires a clear and transparent framework, and as part of that framework, includes a tractable analysis and balancing of various qualities of information from numerous sources (National Research Council (NRC), 1983).

Risk analysis consists of three principal elements: 1) assessment, 2) management (decision-making), and 3) communication (NRC, 1983). Quantitative microbial risk assessment (QMRA) is an iterative process that evaluates the likelihood that adverse health effects will occur following exposure to a pathogenic microorganism or to the medium in which the microorganism occurs (Olivieri et.al., 1986; International Life Sciences Institute (ILSI), 1996; Presidential/Congressional Committee, 1997). QMRA investigations are typically not widely conducted as routine components of reclaimed water investigations and recreational exposure assessments (Olivieri et.al., 1997; Eisenberg et.al. 1999; Soller et.al., 2004). Further, in addition to the exposure and health impact discussions in this paper, QMRAs are applicable to help clarify and support the results of various additional types of investigations such as source investigation and assessments, fate and transport studies, routes and extent (i.e., frequency and magnitude) of exposure, initial screening assessments to investigate and assist describe uncertainty (incomplete data) and variability (heterogeneity) issues, health impact assessments, management option analysis, and policy/regulatory analysis.

The purpose of this paper is to provide information from several examples on the application of QMRA, and how the information was utilized to aid and facilitate decision-making as part of the regulatory process. This paper does not address fate and transport, or microbial source tracking.

2. QUANTITATIVE MICROBIAL RISK ASSESSMENT – BACKGROUND

In general, there are two approaches that are used to characterize the potential human health risks associated with exposure to pathogens in water 1) human health effects (epidemiologic) studies, and 2) risk assessments. Our focus here is on the latter.

Risk assessments, generally estimate risk indirectly based on environmental measurements and mathematical modeling. A Microbial Risk Assessment (MRA) evaluates the likelihood of adverse human health effects that can follow exposure to pathogenic microorganisms or to a medium in which pathogens occur. To the extent possible, the MRA process includes evaluation and consideration of quantitative information; however, it also employs qualitative information as appropriate.

There are generally two types of MRA models: static and dynamic. The fundamental difference between these models is that static models do not account for the unique properties of a dynamic infectious disease process (Table 1). Specifically, in static models, the number of individuals assumed susceptible to infection is not time varying, whereas in dynamic models that number is time varying. Static models assume that the population may be categorized into two or three epidemiological states: a susceptible state, an infected, and sometimes a diseased state. Although any of the individuals can be exposed to the pathogen of interest, only those who are susceptible can become infected. The probability that exposed individuals moving into the infected/diseased state is governed by the dose of the pathogen to which they are exposed and the infectivity of the pathogen. Although a number of environmental sources may expose humans to pathogens, static models typically assume that susceptible individuals are exposed to pathogens from the specific pathway under consideration for the investigation. They therefore do not include the potential interactions and implications of multiple routes of exposure.

Table 1. Comparison of Static and Dynamic Risk Assessment Models.

Static risk assessment model	Dynamic risk assessment model
The number of individuals susceptible to infection is time invariant	The # of individuals susceptible to infection is time variant
Direct exposure (environment-to-person)	Direct (environment-to-person) and indirect exposure (person-to-person)
Individual-based risk	Population-based risk
Potential for secondary transmission of infection or disease is typically not considered or assumed as a constant factor if it is.	Potential for secondary transmission of infection or disease is considered and the magnitude of transmission is a function of susceptible, infected and immune population.
Immunity to infection from microbial agents is typically not considered.	Exposed individuals may not be susceptible to infection or disease because they may already be infected or may be immune from infection due to prior exposure.
Dose-response function is the critical health component.	The dose-response function is important; however, factors specific to the transmission of infectious diseases may also be important.

A dynamic risk assessment model makes assumptions that divide the population into epidemiological states. Individuals move from one state to another based on epidemiologically relevant data (duration of infection, duration of immunity, etc.). Only a portion of the population is in a susceptible state at any point in time, and only those individuals can become infected or diseased through exposure to microorganisms. The probability that a susceptible person moves into an exposed state is governed by the dose of pathogen to which they are exposed; the infectivity of that pathogen; and the number of infected/diseased individuals with whom they may come into contact.

For both dynamic and static representations of the disease process, infectivity as a function of dose (estimated using a dose-response function) is an important factor in estimating risk. The dose-response function is also important in a dynamic microbial risk assessment model; however, other important factors may include person-to-person transmission, immunity, asymptomatic infection, and incubation period. Accounting for these additional factors when estimating risks associated with exposure to pathogenic microorganisms requires a more sophisticated mathematical model than the static model.

As part of the Water Environment Research Foundation (WERF) 2004 development of QMRA tools, the question of convergence using a dynamic versus the static model was investigated. The analysis indicated that, generally, as risk levels of concern of decreased, the static and dynamic model estimates converged (Soller et al., 2004).

3. PATHOGENS OF CONCERN

Conducting an assessment of public health risk associated with exposure to water-borne pathogens requires the selection of representative pathogen(s). The following factors are relevant to selecting pathogens: (1) for waterborne illness or disease to occur, an agent of disease (pathogen) must be present; (2) the agent must be present in sufficient concentration to produce disease (dose); and (3) a susceptible host must come into contact with the dose in a manner that results in infection or disease (Cooper et al., 1996; Cooper, 1991).

Although a wide range of pathogens have been identified in raw wastewater, relatively few types of pathogens appear to be responsible for the majority of the waterborne illnesses caused by pathogens of wastewater origin (Mead et al., 1999). The pathogens of public health concern, based on foodborne disease in the U.S., were identified by the Centers for Disease Control (CDC) (Mead et al., 1999, Scallan et al., 2011). Noroviruses (provisionally known as Norwalk-like viruses) have been reported to account for approximately 60% of the illnesses, of which 60% are estimated to be non-foodborne. Rotavirus accounts for 3.9 million illnesses each year, of which 99% are non-foodborne (Mead et al., 1999). With this background, it follows that many of these pathogens find their way into domestic wastewater.

Review of the CDC research data indicates that 85 to 90 % of all non-foodborne cases (i.e., cases related to other routes of transmission such as waterborne) in the United States are caused by viral pathogens (i.e., enteric viruses). The relative importance of viral pathogens in waterborne transmission of disease is supported by data from the World Health Organization (WHO) (World Health Organization, 1999) and by research conducted over the last 20 years on exposure to waterborne pathogens through recreational activities (Cabelli, 1983; Wade et al., 2003; Soller et al., 2010).

Based on the above discussion of possible pathogens of concern, pathogens known to be present in wastewater, CDC's estimated disease burden in the United States, and those pathogens where treatment plant performance, exposure data, and dose-response data may exist, the following are a representative list of the "pathogens of public health concern" for conducting QMRAs: Human enteric viruses as estimated by norovirus or enterovirus in treated wastewater and a rotavirus dose response; Protozoa as estimated by *Cryptosporidium parvum* and *Giardia lamblia*; and Bacteria as estimated by *E. coli* O157:H7, *Salmonella spp., and Campylobacter spp.* (US EPA, 2012).

4. CASE STUDIES

The following summary covers a number of dynamic and static risk assessments, conducted to assist local and state agencies address regulatory questions, related to the protection of public health following a scientifically defensible, tractable, and quantitative process. The case studies rely on the use of QMRA to inform the regulatory decision making process from a number of perspectives: 1) as part of the State review of potential impacts on receiving water beneficial uses (see Section 4.1), 2) as part of the quantification of potential public health risk relative to review of State water reuse regulations (see 4.2), 3) as part of the information submitted by a publicly owned treatment work (POTW) during preparation of an National Pollutant Discharge Elimination System (NPDES) application and discharge permit consistent with the Clean Water Act (see Section 4.1- Stockton case study, and 4.3), and 4) as part of informing the discussion associated with the interpretation and application of US EPA regulations and guidance (see Section 4.4)

4.1 Recreational Exposure - Population Based Assessment (City of Stockton, CA, Soller et al., 2003)

The City of Stockton, California operates a publicly owned treatment work (POTW) that discharges treated wastewater effluent to the San Joaquin River. At the time of the assessment (i.e., 1996 through 2002), the facility included secondary treatment through stabilization ponds followed by filtration and disinfection between May and October and secondary treatment during the rest of the year. Designated beneficial uses of the river include water contact and non-contact recreation, agricultural supply, and municipal and domestic uses. During the discharge permit renewal process, the California Regional Water Quality Control Board asserted that the winter season discharge “has a reasonable potential to cause a health risk for contact recreation in the San Joaquin River near the vicinity of the discharge.” The QMRA was initiated to determine if the addition of filtration to the facility’s operation during the winter season would substantially reduce the potential public health risk associated with recreation in the river for existing (100-150 million L/d) and potential future (200 million L/d) effluent flows. As a point of reference, U.S. EPA considers water quality standards for freshwater to be protective if a state’s criteria are based on an illness rate equal to or less than 14 illnesses per 1000 recreation events (USEPA 1986 and 2002).

Although modeling the transmission of infectious diseases as a dynamic process requires substantially more data than do static models, dynamic models are able to account for population dynamics and protection from infection due to prior exposures (Eisenberg et al. 1996, 1998, and 2002). In this QMRA, existing hydraulic (Chen et al., 1996) and disease transmission models (Eisenberg et al., 1996) were extended to characterize quantitatively the incremental benefit that tertiary treatment would provide over that provided by secondary treatment during the winter season at the City of Stockton wastewater treatment facility. For the assessment, it was assumed that the incremental benefit is defined as a relative comparison of viral gastroenteritis attributable to the treatment facility for the treatment scenarios investigated.

The results of the investigation suggest that risk of viral gastroenteritis attributable to the treatment facility under the existing treatment scheme is several orders of magnitude below the illness level associated with recreational water quality criteria in the US (US EPA, 2012), and winter tertiary treatment would further reduce the existing risk by approximately 15-50%.

The methodologies employed herein are applicable to other watersheds where additional water treatment is being considered to address public health concerns from recreation in receiving waters. For example, QMRAs using a dynamic model were also conducted for recreational exposure in Newport Bay, California and Mamala Bay, Hawaii.

Newport Bay (Soller et al., 2006)

The State of California identified Newport Bay (Orange County, California) as a waterbody in which the fecal coliform water quality objective for body contact recreation (REC-1) was not being attained. A comprehensive health based evaluation was employed to interpret the impairment of the REC-1 use in Newport Bay. The findings of this study indicate that exceedances of the fecal coliform water quality objectives for the REC-1 use in Newport Bay were temporally sporadic, geographically limited, and most commonly occurred during the time of the year when REC-1 use is low and/or in areas of the Bay where the REC-1 use is low or prohibited by local ordinance.

QMRA dynamic model simulations produced population-level risk estimates for recreation in Newport Bay that were generally below levels considered tolerable by the US EPA (median estimate was 0.9 illnesses per 1000 recreation events). Implementing control measures to reduce pathogen loading to Newport Bay varied in effectiveness relative to estimated risk reduction from recreation (16% to 50%), with the less expensive options providing the greatest estimated reductions in risk. Interpreting the public health implications of fecal indicator data requires a more rigorous and comprehensive approach to evaluating the impairment of the REC-1 beneficial use than solely relying on evaluating exceedances of bacterial based water quality standards.

Mamala Bay (Cooper et al., 1996)

A QMRA dynamic model was utilized to assess the public health risk from recreational exposure to Mamala Bay, Hawaii. Mamala Bay was defined as ocean waters from Diamond Head to Barbers Point, Oahu. More specifically, recreational exposure was evaluated for Waikiki and Ala Moana beaches to examine *Giardia*, *Cryptosporidium*, *Salmonella* and enteroviruses.

Model simulations were performed to test the effects of pathogen contributions from swimmers (shedding), pathogens from sources other than shedding, and order of magnitude increases or decreases in pathogens contributed from the other sources (non-shedding). The results indicate that for the four microorganisms tested at the two beach sites there was very little statistical variation in the results among the recreational exposure investigated as compared to the background prevalence in the population. Further, increasing or decreasing the contribution from non-shedding sources by an order of magnitude did not appear to significantly increase the disease prevalence in the population above background. The models were most sensitive to changes in the background disease transmission rate and to variations in the fraction of the population that moves from infectious and symptomatic conditions to non-infectious and asymptomatic conditions in a given day. The assessment indicated that the risks of contracting an infection by bathing, swimming, surfing, or fishing in Mamala Bay waters are low. At the principal beaches the risk of acquiring an illness from ingestion of contaminated water at the concentrations actually observed in the Study, for example, was found to be little different from the risk for the general population not exposed to Mamala Bay waters. This conclusion appears to be substantiated, incidentally, by the very low incidence of reported cases of disease among both the resident and recreational populations that use the waters of Mamala Bay.

4.2 Water Recycling Exposure - Static Assessment (California Department of Public Health Water Recycling Criteria for food crop exposures, Cooper et al., 2012; Olivieri et al., 2014)

California's water quality standards and treatment reliability criteria for water recycling are contained in the California Department of Public Health's (CDPH) Water Recycling Criteria (Title 22, Division 4, Chapter 3, of the California Code of Regulations). Because of adherence to these criteria, the use of recycled water for agricultural food crop irrigation has a history of safe use (i.e., no evidence of outbreaks attributable to this use, or of increased cases of enteric disease) in California. However, improved knowledge of wastewater treatment effectiveness, changes in agricultural practices, and increased knowledge of the behavior of pathogens and disease have prompted a re-evaluation of the criteria through an expert Panel convened by CDPH. The criteria vary according to the type of agricultural irrigation. For example, for irrigation of food crops eaten raw where there is direct contact between the recycled water and edible portion of the crop, the criteria require tertiary treatment (secondary treatment followed by filtration to achieve a turbidity of ≤2 NTU), and disinfection to produce a 7-day median total coliform level of ≤2.2/100 mL in the recycled water with a CT (i.e., the product of total chlorine residual concentration and the model contact time) of not less than 450 milligram-minutes per liter.

California currently recycles treated wastewater at a volume of approximately 8.0 $x10^8$ m^3 of water per year, with a potential to recycle an additional $1.9x10^9$ m^3 per year. A key challenge in promoting the expansion of water recycling for agricultural purposes, was addressing the perceived concern about whether recycled water produced in conformance with California's Water Recycling Criteria is protective of public health. The Panel found, based on QMRA that the annualized median risks of infection for full tertiary treatment ranges from 10^{-8} to 10^{-4} (for human enteric viruses *Cryptosporidium parvum* and *Giardia lamblia*, and *Escherichia coli* O157:H7) based on the assumption of daily exposure. The Panel found that "risk estimates are consistent with previous CDPH estimates and concluded that current agricultural water recycling regulations do not measurably increase public health risk."

4.3 Recreation and Agricultural Exposure – Static Assessment (City of Vacaville, California, Olivieri et al., 2012; Danielson et al., 2013)

The City of Vacaville is located approximately 30 miles northeast of San Francisco Bay. The City's Easterly Wastewater Treatment Plant (EWWTP) discharges disinfected and dechlorinated secondary effluent ("final disinfected effluent") into the receiving waters of the watershed of the Sacramento-San Joaquin Delta. The QMRA was conducted to support the NPDES permit renewal process and to further clarify and inform stakeholder concerns regarding potential risk of infectious disease to those who recreate in the receiving waters. Both EWWTP influent and final disinfected effluent, as well as 11 receiving water stations, were monitored for various indicator and pathogenic microorganisms. Indicator organisms were sampled twice per month over a 13 month period and included the coliform group; *E. coli; Enterococcus;* male-specific bacteriophage (MS2); and the *Bacteroidales.* Samples for pathogens were collected and assayed seasonally and included, *Giardia* cysts and *Cryptosporidium oocysts;* infectious *Cryptosporidium;* and Norovirus GI and GII. Estimated median annualized risk ranged from 10^{-9} to 10^{-10} for enteroviruses and 10^{-5} to 10^{-7} for parasites for use of secondary disinfected effluent with direct contact and non-contact on agricultural food crops, respectively. All estimates are lower than the 10^{-4} CDPH-assumed level of acceptable infection for recreational exposure. The addition of filtration results in lowering the annualized median risk estimates for the parasites by about 1 log resulting in risk estimates for parasites on the order of 10^{-6} to 10^{-8}.

In addition, the QMRA results indicate that exposure to the local receiving waters present annualized risk levels of 10 to 1000 times (i.e., 1 to 3 logs, base 10) greater than direct exposure to final filtered and disinfected effluent for the various routes of exposure investigated. Further, the results of bacterial indicator monitoring and source tracking investigation coupled with the heavy agriculture and farm land uses adjacent to the sloughs, clearly indicates that predominate sources for these microbial organisms in the receiving water are of non-human origin.

Finally, the 13 month EWWTP and receiving water microbial monitoring program supporting the current QMRA results are consistent with and support the basis for the 2002 CDPH decision regarding seasonal treatment limits for the protection of public health from potential exposure associated with recreation in undiluted effluent, and from golf course and food crop irrigation with treated effluent.

4.4 Recreation Exposure - Static Assessment (Wet weather overflows San Francisco Bay, California, Konnan et al., 2009)

An investigation was carried out to evaluate the impacts of blending practices (i.e, a practice used by some POTWs to manage the treatment plant when flows during wet weather exceed secondary treatment capacity) on the effluent from the East Bay Municipal Utility District's (EBMUD) wastewater treatment plant in Oakland, California and water quality in the receiving water (San Francisco Bay). A key element of the study was a microbial risk assessment (MRA), the focus of which was on quantifying the incremental risk associated with increased concentrations of pathogens measured in the effluent and modeled in the receiving water during blending events. Public health risk was evaluated at selected water contact recreation sites in central San Francisco Bay located within the spatial extent of elevated pathogen concentrations in the Bay during blending, based on a Bay water quality model. In addition, the municipal treatment plant outfall was included as an exposure location. The QMRA used a static risk assessment approach to estimate the potential annualized public health risk associated with exposure to adenovirus and the protozoan *Giardia* spp., since field sampling found elevated concentrations of these pathogens in EBMUD's wastewater treatment plant effluent during blending events relative to non-blending conditions. Pathogen concentrations at recreational exposure locations in the Bay were generated by the water quality model. A total of thirty scenarios were modeled, each representing a unique combination of pathogen, exposure site, and plant condition (i.e., blending vs. not blending). Quantitative data on the level of water contact from recreation at each of the exposure sites were obtained and used to develop annualized risk estimates. The incremental annual number of infections due to blending was estimated based on the number of recreational exposure events per day at each exposure site, the estimates of risk per recreational exposure event under the blending and non-blending scenarios, and an assumed range of annual blending days (zero to 30).

Estimated risks of infection were higher under blending conditions compared to non-blending conditions and the risks of infection by adenovirus were generally higher than *Giardia* spp. With the exception of the worst case outfall location during blending scenario, median risks per recreational exposure event for all of the modeled scenarios were more than an order-of-magnitude below the EPA's illness level associated with recreational water quality criteria. The annualized risk estimates provide an indication of the relative impacts of increased numbers of blending days per year, with zero blending days serving as a baseline level to evaluate the annual number of infections associated with 10, 20, and 30 blending days. While the MRA results showed discernible differences in per event risk between blending and non-blending scenarios, the estimated incremental increase in annual number of infections due to blending was small. Based on the median estimates, recreational exposure at the selected exposure sites resulted in an estimated combined increase of less than one infection annually. The QMRA estimates are based on 107, 30, and 43 recreational exposure events per wet season day for Crown Beach, Aquatic Park, and Treasure Island recreational sites, respectively. Thus the relative impact of 30 blending days per year in terms of increased annualized risk to water contact recreators in central San Francisco Bay appeared small.

5. Value of QMRAs

Within the context of evaluating exposures associated with water recycling and municipal treatment plant discharges, QMRA is a valuable tool to evaluate regulatory standards, to bridge information gaps, and/or to assist a risk manager in making informed choices. In the above investigations, microbial risk assessment methodologies were evaluated to determine their applicability for human exposure to pathogens from wastewater discharges and water recycling.

Extrapolating the results presented to routes of exposure, pathogens, and/or model variants not investigated should be done with caution because microbial risk assessments are agent and scenario specific. Also, the cumulative effects of exposure to multiple pathogens are usually not explicitly investigated. More specifically, QMRA methods should more appropriately be used to derive a matrix of relative risks based on combinations of pathogens representing those of greatest public health concern, treatment processes that are representative of those currently used to achieve receiving water discharge requirements and produce recycled water used for various types of potential exposures (e.g., landscape irrigation, irrigation of food crops), and relevant exposure routes.

Further, multiple analytical laboratory techniques are now available with results expressed in a variety of units (e.g., MPN, CFU, GU, etc.) some of which may not be consistent with available dose response information. For example, a recent QMRA (Bambic et.al, 2011) highlighted the need to harmonize virus units – making consistent the concentration units from water quality testing with the units reported in dose response studies. That study acknowledged that their water samples were analyzed by quantitative polymerase chain reaction (qPCR) for rotavirus, while the dose-response relationship of Ward et al. (1986) was in terms of doses of “Focus Forming Units” (FFU). These seemingly incompatible units were equated using a study-specific ratio of genome:FFU of ~ 2000. In addition, selecting reference pathogens to adequately represent the risk from pathogens potentially present in fecal matter is an important first step as previously described and is consistent with U.S. EPA work (USEPA, 2005).

Given the above complexities and the difficulties associated with interpreting the public health implications of fecal indicator data, a more rigorous and comprehensive approach to evaluating the impairment of the beneficial use should be considered rather than relying solely on evaluating exceedances of bacterial based water quality standards. Such an approach would be consistent with (1) the basic principles of public health engineering regarding the use of sanitary surveys to identify and control potential sources to the maximum extent practicable; and (2) a health based monitoring approach for recreational waters outlined by the WHO (World Health Organization 1999).

Although the risk management process must account for many disparate considerations, to the extent feasible that process should take advantage of the best available scientific information including quantitative risk assessment methodologies to inform public policy. Quantitative risk assessment methods, as described above, offer an explicit description of available data, a clear statement of assumptions, a careful description of the analytical methods utilized to integrate the available data, and a clear statement about uncertainties relative to interpretation of the assessment results. Microbial risk assessment conducted within the context described above offers valuable tool and provides insight to risk managers. Finally, the QMRA applications (i.e., static and dynamic models) have been successfully utilized to inform regulatory decisions regarding NPDES permit discharge requirements, provide clarity to local and State agencies regarding potential public health impacts on beneficial uses (e.g., recreational exposure), and assisted State regulators evaluate the potential public health implications associated with current water recycling regulations.

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