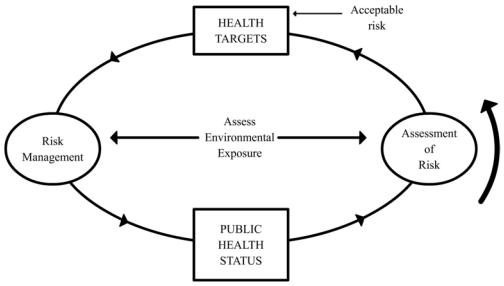

8

Risk assessment

Chuck Haas and Joseph N.S. Eisenberg

This chapter introduces the technique of microbial risk assessment and outlines its development from a simple approach based upon a chemical risk model to an epidemiologically-based model that accounts for, among other things, secondary transmission and protective immunity. Two case studies are presented to highlight the different approaches.

8.1 BACKGROUND

Quantifiable risk assessment was initially developed, largely, to assess human health risks associated with exposure to chemicals (NAS 1983) and, in its simplest form, consists of four steps, namely:

- hazard assessment
- exposure assessment
- dose–response analysis
- risk characterisation.

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The output from these steps feeds into a risk management process. As will be seen in later sections this basic model (often referred to as the chemical risk paradigm) has been extended to account for the dynamic and epidemiologic characteristics of infectious disease processes. The following sub-sections elaborate on the chemical risk paradigm as outlined above.

8.2 CHEMICAL RISK PARADIGM

8.2.1 Hazard assessment

For micro-organisms, hazard assessment (i.e. the identification of a pathogen as an agent of potential significance) is generally a straightforward task. The major tasks of Quantitative Microbiological Risk Assessment (QMRA) are, therefore, focused on exposure assessment, dose–response analysis and risk characterisation. The task of risk management is one of deciding the necessity of any action based upon the risk characterisation outputs, and incorporates significant policy and trans-scientific concerns.

One outcome of the hazard analysis is a decision as to the principal consequence(s) to be quantified in the formal risk assessment. With micro-organisms, consequences may include infection (without apparent illness), morbidity or mortality; furthermore, these events may occur in the general population, or at higher frequency in susceptible sub-populations. Although mortality from infectious agents, even in the general population, cannot be regarded as negligible (Haas *et al*. 1993), the general tendency (in water microbiology) has been to regard infection in the general population as the particular hazard for which protection is required. This has been justified based on a balance between the degree of conservatism inherent in using infection as an endpoint and the (current) inability to quantify the risks to more susceptible sub-populations (Macler and Regli 1993).

8.2.2 Exposure assessment

The purpose of an exposure assessment is to determine the microbial doses typically consumed by the direct user of a water (or food). In the case of water microbiology, this may necessitate the estimation of raw water micro-organism levels followed by estimation of the likely changes in microbial concentrations with treatment, storage and distribution to the end-user (Regli *et al*. 1991; Rose *et al*. 1991). A second issue arising in exposure assessment is the amount of ingested material per ‘exposure’. As a default number, two litres/person-day is used to estimate drinking water exposure (Macler and Regli 1993), although this may be conservative (Roseberry and Burmaster 1992). For contact recreational

exposure, 100 ml/day has often been assumed as an exposure measure (Haas 1983a), but actual data to validate this number are lacking.

8.2.3 Dose–response analysis

It is generally necessary to fit a parametric dose–response relationship to experimental data since the desired risk (and dose) which will serve to protect public health is often far lower than can be directly measured in experimental subjects (at practical numbers of subjects). Hence it is necessary to extrapolate a fitted dose–response curve into the low-dose region.

In QMRA, for many micro-organisms, human dose–response studies are available which can be used to estimate the effects of low level exposure to micro-organisms. In prior work, it has been found that these studies may be adequately described by one of two semi-mechanistic models of the infection process. In the exponential model, which may be derived from the assumption of random occurrence of micro-organisms along with a constant probability of initiation of infection by a single organism (r), the probability of infection (P_I) is given as a function of the ingested dose (d) by:

$$P_I = 1 - \exp(-rd) \tag{8.1}$$

For many micro-organisms, the dose–response relationship is shallower than reflected by Equation 8.1, suggesting some degree of heterogeneity in the micro-organism-host interaction. This can be successfully described by the beta-Poisson model, which can be developed from Equation 8.1 if the infection probability is itself distributed according to a beta distribution (Furumoto and Mickey 1967a,b; Haas 1983b). This model is described by two parameters, a median infectious dose (N_{50}) and a slope parameter (α):

$$P_I = 1 - \left[1 + \frac{d}{N_{50}} \left(2^{1/\alpha} = 1 \right) \right]^{-\alpha} \tag{8.2}$$

Figure 8.1 depicts the effect of the slope parameter on the dose–response relationship; in the limit of $\alpha \to \infty$, Equation 8.2 approaches Equation 8.1.

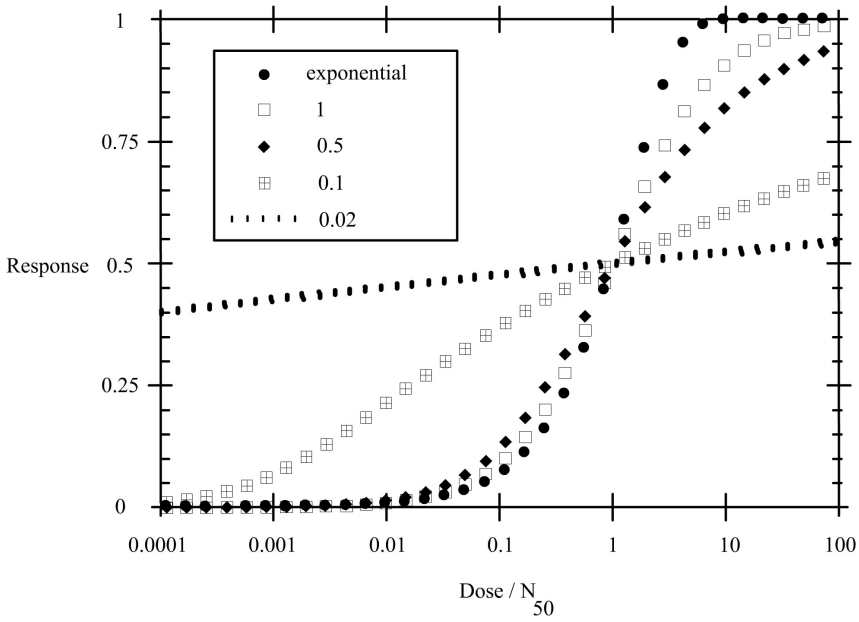

Figure 8.1. Comparison of exponential and beta-poisson dose–response functions.

The exponential and beta-Poisson models are two dose–response relationships that can be developed from biologically plausible assumptions about the infection process (Table 8.1 outlines the best-fit dose–response parameters for these models for a number of human pathogens). A general framework for plausible models can also be derived.

In addition to such quasi-mechanistic models, a variety of empirical models are possible, three models which have been used (primarily in chemical risk assessment), are the log-logistic, the Weibull, and the log-probit.

Generally, several models may fit available data in a statistically acceptable sense, and yet provide very different estimates for the risk at an extrapolated low dose. This situation is one that has frequently been encountered in chemical risk assessment (Brown and Koziol 1983). In QMRA, it may be possible to test the potential appropriateness of different dose–response functions by validating with outbreak data.

Given a set of dose–response data, i.e. exposure of populations to various doses of micro-organisms and measurement of response (such as infection), the best fitting parameters of a dose–response relationship may be computed via standard maximum likelihood techniques. The method has been illustrated for human rotavirus (Haas *et al*. 1993; Regli *et al*. 1991) and protozoa (Rose *et al*.

1991). Confidence limits to the parameters can then be found, and used as a basis for low-dose extrapolation. It should be noted, however, that in general dose–response studies have been conducted on healthy adults and may not, therefore, reflect the response of the general population.

Table 8.1. Table of best-fit dose–response parameters (human)

Organism	Exponential	Beta Poisson		Reference
	k	N_{50}	α	
Poliovirus I (Minor)	109.87			Minor *et al*, 1981
Rotavirus		6.17	0.2531	Haas *et al*. 1993; Ward *et al*. 1986
Hepatitis A virus[a]	1.8229			Ward *et al*. 1958
Adenovirus 4	2.397			Couch *et al*. 1966
Echovirus 12	78.3			Akin 1981
Coxsackie[b]	69.1			Couch *et al*. 1965; Suptel, 1963
Salmonella[c]		23,600	0.3126	Haas *et al*. 1999
Salmonella typhosa		3.60×10^6	0.1086	Hornick *et al*. 1966
Shigella[d]		1120	0.2100	Haas *et al*. 1999
Escherichia coli[e]		8.60×10^7	0.1778	Haas *et al*. 1999
Campylobacter jejuni		896	0.145	Medema *et al*. 1996
Vibrio cholera		243	0.25	Haas *et al*. 1999
Entamoeba coli		341	0.1008	Rendtorff 1954
Cryptosporidium parvum	238			Haas *et al*. 1996; Dupont *et al*. 1995
Giardia lamblia	50.23			Rose *et al*. 1991

[a] dose in grams of faeces (of excreting infected individuals)
[b] B4 and A21 strains pooled
[c] multiple (non-typhoid) pathogenic strains (*S. pullorum* excluded)
[d] *flexnerii* and *dysenteriae* pooled
[e] Nonenterohaemorrhagic strains (except O111)

8.2.4 Risk characterisation

The process of risk characterisation combines the information on exposure and dose–response into an overall estimation of likelihood of an adverse consequence. This may be done in two basic ways. First, a single point estimate of exposure (i.e. number of organisms ingested) can be combined with a single point estimate of the dose–response parameters to compute a point estimate of risk. This may be done using a 'best' estimate, designed to obtain a measure of central tendency, or using an extreme estimate, designed to obtain a measure of consequence in some more adversely affected circumstance. An alternative approach, which is currently receiving increasing favour, is to characterise the

full distribution of exposure and dose–response relationships, and to combine these using various tools (for example, Monte Carlo analysis) into a distribution of risk. This approach conveys important information on the relative imprecision of the risk estimate, as well as measures of central tendency and extreme values (Burmaster and Anderson 1994; Finkel 1990).

One important outcome of the risk characterisation process using a Monte Carlo approach is the assessment of the relative contribution of uncertainty and variability to a risk estimate. Variability may be defined as the intrinsic heterogeneity that leads to differential risk among sectors of the exposed group, perhaps resulting from differential sensitivities or differential exposures. Uncertainty may be defined as the factors of imprecision and inaccuracy that limit the ability to exactly quantify risk. Uncertainty may be reduced by additional resources, for example devoted to characterisation of the dose–response relationship. Variability represents a lower limit to the overall risk distribution.

Two aspects of risk characterisation deserve further comment. In general, all available dose–response information for micro-organisms (human or animal) pertains to response to single (bolus) doses. In actual environmental (or food) exposures, doses may occur over time (or may even be relatively continuous). In the absence of specific data on the impact of prior exposure on risk, the assumption used in projecting risk to a series of doses has been that the risks are independent (Haas 1996).

8.2.5 Risk management

The results of a risk characterisation are used in risk management. The understanding of appropriate action levels for decision-making with respect to micro-organisms is still at an early stage (see Chapter 10). However, in the case of waterborne protozoa, it has been suggested (in the US) that an annual risk of infection of 0.0001 (i.e. 1 in 10,000) is appropriate for drinking water (Macler and Regli 1993).

8.3 *CRYPTOSPORIDIUM* CASE STUDY

This case study follows through the process described in the previous section and details a microbiological risk assessment focusing on *Cryptosporidium* in a US city. New York City has a central water supply reservoir that receives the flow from two watersheds (*Watershed C and Watershed D*). Oocyst levels have been determined for both watersheds since 1992. *Cryptosporidium* was chosen as the organism of interest since it is currently the pathogen most resistant to disinfection (with minimal inactivation by free chlorine alone: Finch *et al*. 1998;

Korich *et al*. 1990; Ransome *et al*. 1993). Hence, for *Cryptosporidium*, the effluent from the final water supply reservoir provides a reasonable starting point for estimating oocysts in the water as consumed.

To estimate the potential level of infection from *Cryptosporidium* present in the watershed supplies, the following inputs are needed:

- water ingestion per day (V)
- oocyst concentration at point of ingestion (C)
- dose–response relationship for *Cryptosporidium* f(V × C)

In this instance, in accordance with a number of prior risk assessments, each day of exposure (consumption of water) is considered to result in a statistically independent risk of infection (Haas *et al*. 1993; Regli *et al*. 1991).

8.3.1 Input exposure variables

Tap-water ingestion was modelled using the log-normal distribution for total tap-water consumption developed by Roseberry (Roseberry and Burmaster 1992). The natural logarithm of total tap-water consumption in ml/day is normally distributed with a mean of 7.492 and standard deviation of 0.407 (corresponding to an arithmetic mean of 1.95 l/day).

Initial examination of the time series of oocyst levels monitored to date from the two watersheds indicates a number of interesting features (Figure 8.2), namely:

- The levels of oocysts are quite variable, as is common for many microbial data sets.
- The densities appear to be higher during the earlier portion of the data record than in the more recent part of the data record (for reasons that are unclear).
- There are a substantial number of samples where no oocysts were detected. The mean detection limit for these non-detects was 0.721 oocysts/100 l.

The overall mean oocyst concentration (treating the ‘non-detects’ as zero’s) was 0.26 and 0.31 oocysts/100 l for the watershed C and watershed D locations, respectively. Of the 292 samples taken at each location, only 45 samples at watershed C and 48 samples at watershed D were above individual daily detection limits. Of these samples, only 18 and 21, respectively, were above 0.721 oocysts/100 l (the average detection level for the non-detects). This

pattern is not unusual in protozoan monitoring data, and it presents a level of complexity in assessing the risk posed by exposure to these organisms.

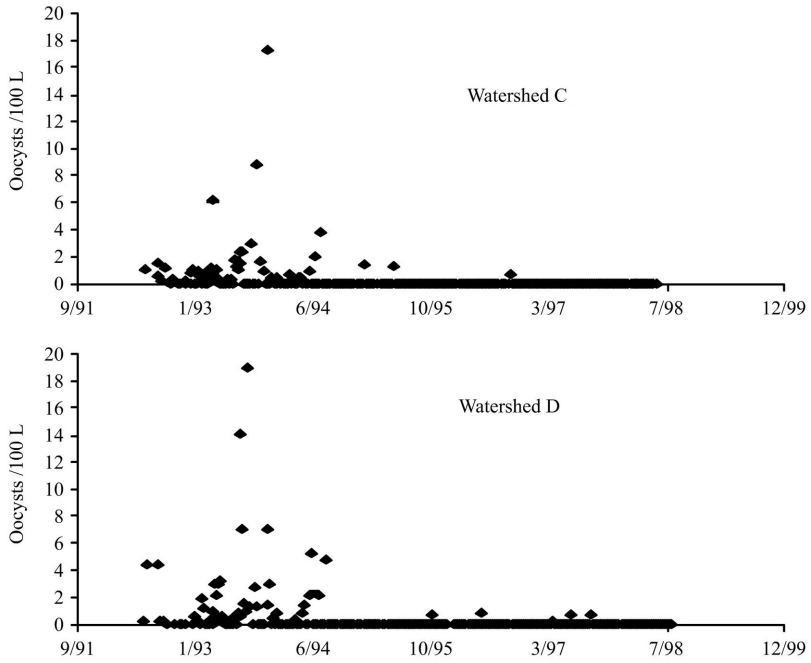

Figure 8.2. Total oocyst concentration in reservoir raw water samples.

The significant number of samples with concentrations close to or below the average detection limit must be taken into account when estimating mean oocyst densities and distribution. There are several methods that may be used when dealing with below-detection-limit (BDL) data (Haas and Scheff 1990). Two basic approaches are employed here.

- Observations that are below the detection limit are treated as if they had values equal to the detection limit, half the detection limit, or zero. The arithmetic mean of the revised data is then computed by simple averaging. These alternatives are called ‘fill in’ alternatives.
- The method of maximum likelihood is used. In this approach, the data are presumed to come from a particular distribution (e.g. log-normal), and standard methods for analysing data with a single censoring point are used. A likelihood function is

formulated with a contribution equal to the probability density function for all quantified values, and equal to the cumulative distribution function (up to the detection limit) for all BDL values. The values of the distribution parameters that maximise the resulting likelihood are accepted as the best estimators.

To develop the distribution for oocyst concentrations at the point of ingestion, all data from the two watersheds were examined. Using maximum likelihood, and treating all observations less than or equal to 0.721 oocysts/100 l as being censored (for all censored observations, 0.721/100 l was regarded as being the detection limit), the parameters of log-normal distributions were determined.

Table 8.2 shows the parameters of the best fitting log-normal distributions to the entire data record at each station. There is some underprediction at the extreme tails of the distribution; however, in general the fit is adequate. Investigation of alternative distributions (gamma, Weibull, and inverse Gaussian) did not yield fits superior to the log-normal distribution. The goodness of fit to the log-normal was acceptable as judged by a chi-squared test.

Table 8.2. Mean and standard deviation of best-fitting normal distribution for natural logarithm of oocyst levels (/100 l) in reservoir samples (January 1992 to June 1998)

	Watershed C	Watershed D
Mean natural logarithm	–2.752	–3.210
Std. deviation of natural log	1.828	2.177

Table 8.3 summarises the arithmetic average from both watersheds, using maximum likelihood and the various fill-in procedures (for 1992 and 1998, these averages are for portions of the year). The ‘imputed arithmetic mean’ is computed from the maximum likelihood estimates (MLEs). In more recent years, it was not possible to estimate the maximum likelihood mean densities at both locations and all times, since too few (<2) observations above the detection limit were available.

Table 8.3. Summary of mean oocyst levels (/100 l) estimated by different methods

	All years	1992	1993	1994	1995	1996	1997	1998*
Watershed C								
Imp. arith mean	0.33	0.62	1.36	0.26	0.16			
Detection limit	0.85	0.72	1.46	0.78	0.73	0.70	0.72	0.72
Half det limit	0.55	0.59	1.30	0.48	0.39	0.36	0.36	0.36
Zero det limit	0.25	0.46	1.13	0.18	0.05	0.01	0	0
Watershed D								
Imp. arith mean	0.43	1.80	1.35	0.47				
Detection limit	0.89	1.14	1.55	0.91	0.70	0.70	0.69	0.72
Half detection	0.60	0.96	1.41	0.62	0.36	0.36	0.36	0.36
Zero det limit	0.30	0.78	1.26	0.33	0.01	0.01	0.02	0

* Jan – June Imp. – Imputed det. - detection

The bias due to 'fill-in' methods using the detection limit and half the detection limit is quite evident in the more recent years, where the oocyst levels were generally below detection. Both of these 'fill-in' methods may overestimate total oocyst concentration in the source water. Regardless of the methods used, it is apparent that 1992 and 1993 had higher average oocyst levels than in more recent years.

In order to assess exposure, the concentrations of oocysts from each watershed were flow-weighted (to allow for relative contributions) and then combined.

The dose–response relationship for infection of human volunteers with C. parvum oocysts has been found to be exponential with a best-fit dose–response parameter (k) equal to 238 (Table 8.1). The confidence distribution to the dose– response parameter k can be determined by likelihood theory (Morgan 1992). The confidence distribution to the natural logarithm of k is then found to be closely approximated by a normal distribution with mean of 5.48 and standard deviation of 0.32.

8.3.2 Results

Given a single value of water consumption (V), oocyst concentration (C), and the dose–response parameter (k), the risk of infection to an individual can be calculated. To consider the distribution of risk, which incorporates uncertainty and variability in each of the input parameters, this calculation needs to be performed a large number of times (Monte Carlo analysis). In this technique a new set of random samples (for water consumption, oocyst concentration at each location, and the dose–response parameter) is obtained, and then individual

calculations using these sets of random samples are combined to reveal an estimated distribution of risk.

Two types of results are presented below. First, the daily risk estimate is calculated for each individual year (to observe trends in risk over time), given a single water dose, dose–response parameter, and average oocyst concentration. Four oocyst concentrations are used, representing the different methods for considering data points below the detection limit. The purpose of this exercise is to observe trends in the risk estimate over time. The second set of results shows the range of estimated risk, taking into account uncertainty in all of the input parameters. This range is generated using the combined data from 1992–8.

8.3.2.1 Point estimates

Point estimates for the daily risk of infection from *Cryptosporidium* are presented in Table 8.4. The four columns represent different methods used to determine the average oocyst concentration, i.e. maximum likelihood and by the three 'fill in' methods. A figure of 1.95 l/day was used for the amount of water consumed and k was set equal to 238. The calculation was done using both the total (1992–8) data set and for each year individually.

Table 8.4. Computed point estimates for the daily risk of infection from *Cryptosporidium* ($\times 10^{-5}$)

	Imputed arith. mean	Fill in methods		
		Detection limit	Half detection limit	Zero detection limit
All Years	3.2	7.1	4.7	2.3
1992	10.7	7.8	6.5	5.3
1993	10.8	12.2	10.9	9.7
1994	3.1	6.9	4.6	2.2
1995	–	5.7	3.0	0.2
1996	–	5.7	2.9	0.1
1997	–	5.6	2.9	0.1
1998*	–	5.6	2.9	0

* (Jan – June)
(–) could not be estimated since fewer than two quantified observations are available

8.3.2.2 Monte Carlo simulation

While useful, point estimates of risk do not reveal the degree of uncertainty in the risk estimate. To do this, Monte Carlo simulations are necessary. Summary statistics on 10,000 iterations of the Monte Carlo model are shown in Table 8.5.

For this computation, the entire (1992–8) oocyst monitoring database was used as the water density distribution. The mean individual daily risk is estimated as 3.42×10^{-5}.

It should be noted that the results of the Monte Carlo analysis bracket the range of point estimates observed by considering each year's data set separately, whether maximum likelihood or 'fill-in' methods are used.

Table 8.5. Summary of Monte Carlo trials. Daily risk of *Cryptosporidium* infection ($\times 10^{-5}$)

Statistic	Individual daily risk
Mean	3.4
Median	0.7
Standard deviation	19.8
Lower 95% confidence limit	0.034
Upper 95% confidence limit	21.9

As part of this computation, a sensitivity analysis was conducted. The rank correlation of the individual daily risk with the various input parameters was computed. The densities of pathogens in the two effluent flows from the reservoir were found to have the greatest correlation with the estimates daily risk. The other inputs (water consumption and dose–response parameter) contributed only a minor amount to the uncertainty and variability in the estimated risk. Attention, therefore, should be paid primarily to obtaining better (more precise) estimates of the effluent oocyst concentrations.

8.3.3 Caveats

The above risk assessment has a number of caveats that should be taken into account when developing a decision based on these results.

- use of healthy volunteer data (based upon a single strain of *Cryptosporidium*)
- no account of secondary infection
- no data on oocyst viability or infectivity
- poor oocyst recovery rates
- choice of endpoint (illness may be a more important endpoint than infection).

8.3.4 Case study conclusions

An annual risk of infection of 1 in 10,000 (which has been suggested by the EPA as an acceptable level for drinking water exposure to an infectious agent) corresponds to a daily risk of 2.7×10^{-7} per person. This is below the lower 95% confidence limit to the estimated daily risk for New York based upon the calculations above. It is also below the point estimates for risk when individual years of data are treated separately. Hence, based on the assumptions used, the current risk of cryptosporidiosis infection would appear to be in excess of the frequently propounded acceptable risk level.

Microbial risk assessments should be coupled with investigation of potential future treatment decisions and watershed management strategies. For example, if information on the performance of such strategies with respect to reduction of oocyst levels is available, then the potential impact on microbial infections can be assessed. Given standard treatment efficiencies, the addition of a properly functioning water filtration plant would reduce the estimated daily and annual risk of *Cryptosporidium* infection by a factor of 100.

8.4 A DYNAMIC EPIDEMIOLOGICALLY-BASED MODEL

As outlined in the previous sections, attempts to provide a quantitative assessment of human health risks associated with the ingestion of waterborne pathogens have generally focused on static models that calculate the probability of individual infection or disease as a result of a single exposure event (Fuhs 1975; Haas 1983b; Regli *et al*. 1991). The most commonly used framework is based upon a chemical model and, as such, does not address a number of properties which are unique to infectious disease transmission, including:

- secondary (person-to-person) disease transmission
- long- and short-term immunity
- the environmental population dynamics of pathogens.

The limitations of treating infectious disease transmission as a static disease process, with no interaction between those infected or diseased and those at risk, has been illustrated in studies of *Giardia* (Eisenberg *et al*. 1996), dengue (Koopman *et al*. 1991b), and sexually transmitted diseases (Koopman *et al*. 1991a). The transmission pathways for environmentally mediated pathogens are complex. These disease processes include person-to-person, person-to-fomite

to-person, person-to-water-to-person as well as food routes for those pathogens that only have human hosts, and they include animal–animal or animal–human pathways for those that have animal reservoirs. To understand the role that water plays in the transmission of enteric pathogens and to estimate the risk of disease due to drinking water within a defined population, it is important to study the complete disease transmission system.

As mentioned previously, models using the chemical risk paradigm are static and assess risks at the individual level; i.e. the risk calculation is the probability that a person exposed to a given concentration of pathogens will have an adverse health effect. The underlying assumption in this calculation is that disease occurrences are independent; that is, the chance of person A becoming infected is independent of the prevalence of disease within the population. Although this assumption is valid for disease associated with chemical exposure, in general, it is not universally appropriate for infectious disease processes. The risk of person A becoming infected is not only dependent on his direct exposure to environmental pathogens but also on exposure to other currently infected individuals (group B). Some of the group B individuals may have been infected from a previous exposure to an environmental pathogen. Therefore, in addition to direct risks of exposure, person A is indirectly at risk due to any previous exposures from group B. One implication of this secondary infection process is that risk is, by definition, manifested at a population level. Specifically, an individual is not only at risk from direct exposure to a contaminated environmental media, but also from interactions within the population that can result in exposures to infected individuals. Another implication of this secondary infection process is that risk calculations are dynamic in nature; i.e. the overall risk calculation is based not only on current exposures to a contaminated media, but also on all subsequent secondary infections.

The existence of other epidemiological states of the disease process may also affect risk estimates; e.g. post-infection status that accounts for previous exposure to the pathogen, and a carrier status that accounts for those who are asymptomatic but infectious. Post-infection status may take on different forms from long-term and complete protection to short-term and partial protection. Therefore, at any given time there may exist a portion of the population that is not susceptible to disease. Moreover, the protected portion of the population will vary in time depending on the prior prevalence levels. Asymptomatic carriers provide another potential source of infection through contact with the susceptible portion of the population. This portion of the population also varies in time.

8.5 CASE STUDY: ROTAVIRUS DISEASE PROCESS

Given the discussion above, we can conceptualise an epidemiologically-based characterisation of risk by dividing the population into distinct states with respect to disease status. States may include susceptible, diseased (infectious and symptomatic), immune (either partial or complete), and/or carrier (infectious but asymptomatic). Further, it can be understood that members of the population may move between states. Factors affecting the rate at which members move between states include:

- the level of exposure to an environmental pathogen;
- the intensity of exposure to individuals in the infectious or carrier state;
- the temporal processes of the disease (e.g. incubation period, duration of disease, and duration of protective immunity, etc.).

This conceptual model is inherently dynamic and population-based; i.e. the risk of infection is manifested at the population level. Thus, consistent with the above concepts, the initial steps prescribed by the infectious disease framework are to identify the important states for a given pathogen or class of pathogens and then develop a diagram of causal relationships among these states. From an epidemiological point of view, the population is divided into distinct states with respect to disease. Historically, when developing these types of compartmental models, members of a population have been classified as susceptible, infected, or recovered. For a pathogen such as rotavirus, however, a simple 'susceptible–infected–recovered' type model may not be sufficient to characterise the movement of the population between states. A more detailed model structure is motivated by the following properties:

- Some protection can be attained after exposure to rotavirus; however, this protective state appears to be neither absolute nor long-term; and
- It is well documented that it is possible (and in fact is common) to be infected with rotavirus without demonstrating the symptoms of the disease.

From these properties, one possible categorisation of the population with respect to the rotavirus disease process is:

- a susceptible state (S), defined by individuals susceptible to infection
- a carrier state (C), defined by individuals who are infectious but not symptomatic
- a diseased state (D), defined by individuals who are symptomatic and infectious
- a post-infection state (P), defined by individuals who are not infectious and not susceptible due to (limited and short-term) immunity.

Members of a given state may move to another state based on the causal relationships of the disease process. For example, members of the population who are in the susceptible state may move to the diseased state after exposure to a pathogenic agent. This is shown in Figure 8.3.

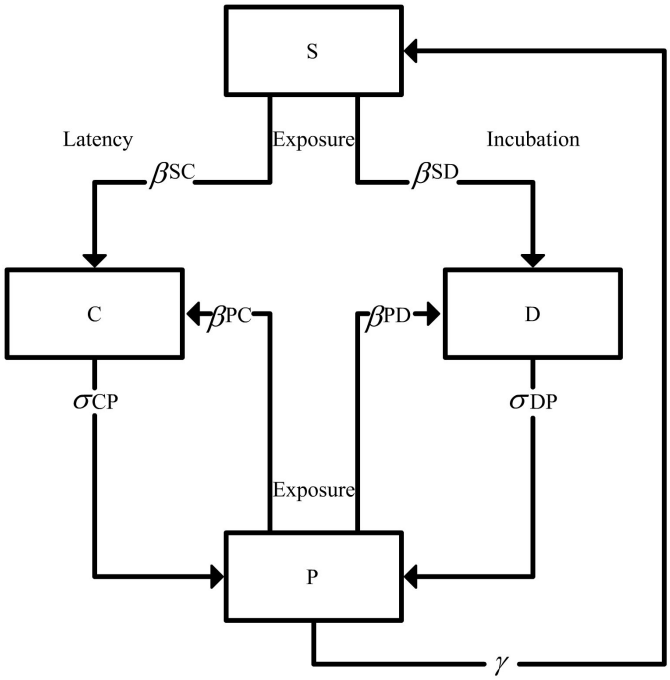

Figure 8.3. Conceptual model for rotavirus. (State variables: **S** = Susceptible = Not infectious, not symptomatic; **C** = Carrier = Infectious, not symptomatic; **D** = Diseased = Infectious, symptomatic; **P** = Post Infection = Not infectious, not symptomatic, with short-term or partial immunity.)

To describe the epidemiology of rotavirus, the conceptual model includes both state variables and rate parameters. State variables (S, C, D, and P) track the number of people that are in each of the states at any given point in time, and are defined such that S + C + D + P = N (the sum of the state variables equals the total population). The rate parameters determine the movement of the population from one state to another. In general, the rate parameters are denoted as β, σ, and γ with appropriate subscripts, where:

- β is the rate of transmission from a non-infectious state, S or P, to an infectious state, C or D. These transmission rate parameters describe the movement between states due to both primary (drinking water, for example) and secondary (all other) exposure to rotavirus;
- σ is the rate of recovery from an infectious state, C or D, to the post-infection state, P; and
- γ is the rate of movement from the post-infection state (partial immunity), P, to the susceptible state, S.

The rate parameters may be determined directly through literature review, may be functions of other variables that are determined through literature review, or may be determined through site-specific data where possible and appropriate. One technical aspect of the approach described is that the distribution of time that members of the population spend in each of the states is assumed to be exponential (this may not always be the case and can easily be addressed; see for example Eisenberg *et al*. 1998).

The model describes movements of the population between states. Consider the susceptible portion of the population during a particular point in time. As shown in Figure 8.3, upon exposure to rotavirus three processes affect the number of susceptible individuals within the population:

- some members of the population will move from the susceptible state S to the carrier state C (at rate β_{SC})
- some members will move from the susceptible state S to the diseased state D (at rate β_{SD})
- other members of the population will move from the post-infection state P back to the susceptible state S (at rate γ).

Analogous processes account for movement of the population between all of the states shown in Figure 8.3. Mathematical details of this model are described in detail elsewhere (Eisenberg *et al*. 1996, 1998; Soller *et al*. 1999).

8.5.1 Implementation

Using a modified version of the ILSI (International Life Sciences Institute) microbial risk framework, the implementation of a conceptual model, such as the rotavirus model, to assess the associated human health risks follows a three step process; problem formulation, analysis, and risk characterisation (ILSI 1996). This process is summarised graphically in Figure 8.4.

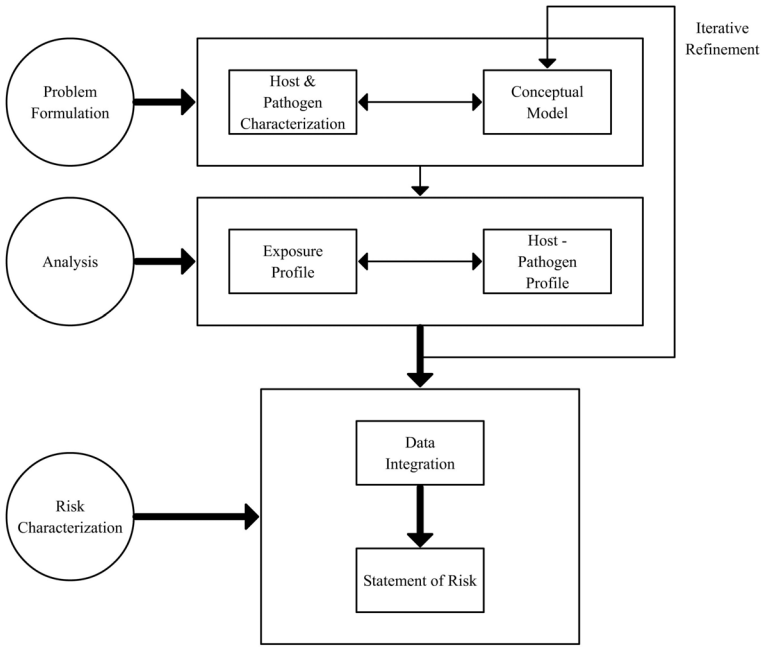

Figure 8.4. Schematic application of the ILSI framework.

8.5.1.1 Problem formulation and analysis

In addition to the development of a conceptual model in the problem formulation phase, a literature review is generally conducted to obtain relevant data. Initial host and pathogen characterisations are also developed.

The goal of the analysis phase is to link the conceptual model with the risk characterisation. This process is carried out by summarising and organising the

data obtained from the problem formulation, resulting in an exposure- and host-pathogen profile that succinctly summarises data relevant to the specific problem.

8.5.1.2 Risk characterisation

In the risk characterisation phase, the exposure and host pathogen profiles are integrated to quantify the likelihood of adverse health effects due to the exposure of microbial contaminants, within the context of the uncertainties in the data and the assumptions used in the quantification process. The risk characterisation also features a data integration step. As described previously, the conceptual model is composed of both state variables and rate parameters. Data integration is the process by which the rate parameters are quantified in terms of probability distributions using available data as a foundation. Once the data integration step is complete, a series of simulations is conducted. A Monte Carlo simulation technique is incorporated to account for the uncertainty and variability inherent in this environmental system. The result of the simulations is a statement of risk or relative risk associated with the specific problem being addressed. Figure 8.5 illustrates how the results of these simulations can be represented.

Box plots were used to summarise each of the four scenarios shown in the graph. The first two scenarios represent the average daily prevalence of a hypothetical baseline condition for children and adults respectively. The third scenario represents children exposed to an increased contamination in drinking water compared with the baseline, and the fourth scenario represents children exposed to a decreased contamination. It is important to keep in mind that this graph is for illustrative purposes only and does not represent an actual risk assessment. With this in mind, the following information can be obtained from this plot:

- the degree of uncertainty associated with each scenario is quite large
- children experience a greater disease burden than adults
- even for very low levels of water contamination an endemic condition exists.

A detailed description of the data integration and risk characterisation processes is summarised in Eisenberg *et al*. (1996).

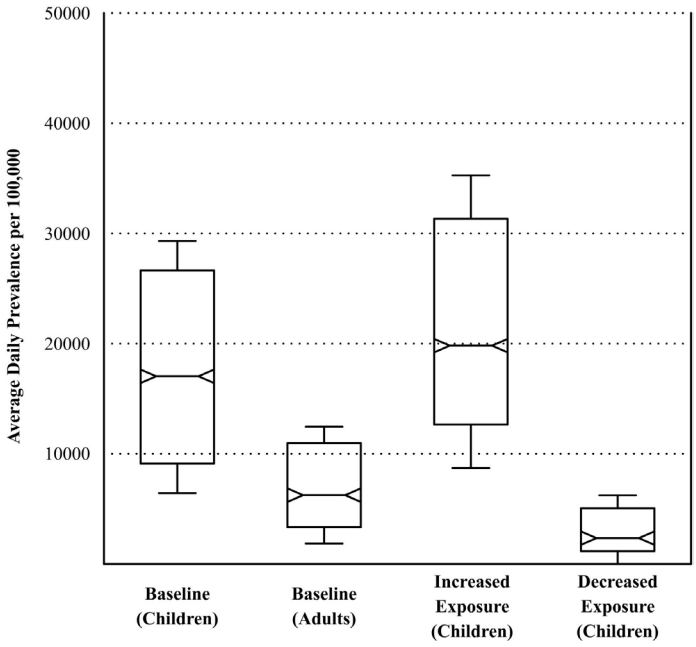

Figure 8.5. Comparison of average daily prevalence for children (1), adults (2), under baseline conditions, and for children exposed to both higher levels (3) and lower levels (4) of contamination in drinking water.

8.6 DISCUSSION

A comprehensive risk assessment methodology should account for all the important processes that affect the resultant risk estimate. One important property of an infectious disease process is the ability of an infected person to infect a susceptible person through direct or indirect contact. To rigorously incorporate this aspect of the disease transmission process, the risk calculation must account for these indirect exposures through contacts with infected individuals. The post-infection process is another property that can affect the risk estimate, since at any given time there is a group of individuals that are not susceptible to reinfection (due to previous exposures to the pathogen).

While the infectious disease process is inherently population-based and dynamic, there may be times when simplifying assumptions may be made, and the chemical risk paradigm may be appropriate. One valuable feature of the methodology presented in the rotavirus case study is that the structure can

collapse into a framework analogous to the chemical risk framework (seen in previous sections) when the secondary infection rate is negligible, protection from future infection due to pathogen exposures is unimportant, and the infection process is static.

Dynamic disease process models have been used in a variety of applications. For example, Eisenberg *et al*. (1998) used this methodology to study the disease dynamics of a *Cryptosporidium* outbreak. In that study, the outcome was known and was used to determine the conditions that may have accounted for the specific outbreak. In another investigation, the same methodology was used to explore the uncertainties in assessing the risk of giardiasis when swimming in a recreational impoundment using reclaimed water (Eisenberg *et al*. 1996). In both of these studies the dynamic, population-based modelling framework was a valuable tool for providing information about the disease process in the context of uncertainty and variability.

8.7 IMPLICATIONS FOR INTERNATIONAL GUIDELINES AND NATIONAL REGULATIONS

In conjunction with epidemiology and other data sources, risk assessment can be a very powerful tool. As well as being used in partnership with epidemiology it can also provide useful insights into areas such as rare events and severe disease outcomes where epidemiology is not appropriate. The ease with which parameters can be changed within a risk assessment makes it ideal to inform both international guidelines and standards derived from specific national circumstances. It can also be used to test 'what if' scenarios, which may help target management interventions. However, the technique does have limitations and it is vital that assumptions are calibrated against real data and it is not seen simply as a substitute for other techniques. As with any model the outputs are, at best, only as good as the inputs.

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