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A Literature Survey on the Assessment of Microbiological Risk for Drinking Water

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Contents

Abstract

This literature study introduces the main ingredients of quantitative risk analysis (QRA) for pathogenic microorganisms in drinking water: hazard analysis, exposure assessment, the assessment of dose-response relations, and risk characterization.
While QRA potentially rationalizes the processes of setting environmental standards and assessing the severity of microbial contamination, the availability of reliable quantitative data becomes crucial. As such, QRA has the potential of growing into an important guidance force within the fields of drinking water quality control and public health.
Opportunities for the implication of QRA into quality control procedures are discussed, special attention is given to the Hazard Analysis Critical Control Point (HACCP) system, since this concept provides a possible framework for the embedding of QRA into process control of drinking water production facilities. The topics of risk perception and acceptance are discussed because of their relevance for defining the framework within which QRA operates (defining the choices, setting limits).

Summary

The dutch drinking water is assumed safe for the consumer. The drinking water quality assurance system is based on the maintenance of maximum concentrations for various parameters. As far as microorganisms are concerned, the main standards are those for indicator organisms for faecal contamination. The basic assumption here is that pathogenic microorganisms are usually of faecal origin.
Recent developments have put this quality assurance practice under increasing strain. Outbreaks of drinking water related diseases have occurred in places where the drinking water met with current microbiological standards (Melnick and Gerba, 1979; Craun, 1981; Lippy and Waltrip, 1984; O'Neil et al., 1985). The quality standards also do not allow for testing of opportunistic pathogens, microbial toxins, allergens, etc. Moreover, correlation between the occurrence of pathogenic organisms and indicator organisms may be absent, especially when "emerging" pathogens, like *Cryptosporidium*, are concerned. Compared to indicator organisms, this latter organism also appears to have a greater resistance to chemical disinfection.
At present, assays are available for many pathogenic microorganisms, enabling direct testing for pathogens instead of looking for indicator organisms. In addition to this, the prediction of health risks via dose-effect modelling is gaining in importance, especially in the U.S.
For a small number of known pathogens dose-response experiments have been performed on human volunteers, sometimes as long ago as 40 years. In these experiments the subjects have been exposed to different concentrations of a pathogenic microorganism, and the fraction that develops infection is scored as a function of the amount of organisms. Pathogen concentrations must be high enough to ensure sufficiently high frequencies of effects (infection, or mild symptoms) so that the necessary number of subjects in these expensive experiments is kept as low as possible.
The concentrations of these organisms in the drinking water are lower by many orders of magnitude. Application of the laboratory data to estimate the probability of infection at these very low concentrations involves extrapolation. For this purpose, a mathematical model can be used. A model may be built by making certain quite general assumptions about the process of infection, and translating these assumptions into a mathematical equation. A few models are introduced in the present report (chapter 4). If a model fits well to the experimental data, it is accepted for use in risk assessment.
For the very low doses generally occurring in drinking water, the probability of infection will be very low as well. Too low to allow direct experimental verification. The model now offers the opportunity to estimate the health risk, also at these extremely low doses. An important property of the used models is the absence of a threshold: with decreasing dose the probability of infection decreases steadily, but no matter how

low the (mean) dose, there always remains a nonzero probability of infection. The satisfactory fit to experimental data does not allow to rule out the possibility that a single microorganism may be capable of causing infection in at least part of the exposed population.

When there is a general consensus about the maximum acceptable health risk for a certain pathogenic organism, the dose-response relation may be utilized to translate this risk level to a maximum acceptable concentration in the drinking water.

In the Netherlands, there is at present no guideline for such a level of acceptance based on health risk. The level of 10^{-4} for the individual annual probability of infection, as used by USEPA, may be useful in this respect. Starting from what little information is available, this assumption leads to probabilities of dying from exposure to pathogenic organisms that are in reasonable agreement with the guidelines used for dangerous substances (VROM, 1989). The variation between different pathogenic species is considerable, however, see table 5.1 and section 5.1.5.

Since infection precedes illness and possibly death, the probability of infection may be treated as a worst case estimate for at least the risk of illness. Using the reference level of 10^{-4} for the annual individual probability of infection, maximum concentrations may be calculated for various organisms in drinking water.

For many organisms the probability of infection per ingested organism (see 5.1.1, the linear approximation at low doses) appears to be so high that the maximum concentrations are below the lowest measurable values. For *Cryptosporidium* 500 samples of 2000 liters each would be needed to make a reasonably accurate estimation of the allowed concentration (7×10^{-6} per liter) (Regli et al., 1991). Therefore a monitoring program must be based upon measurements in the raw, untreated water. The drinking water concentrations must then be calculated, by allowing a (estimated) removal efficiency of the considered treatment process. In order to enable reliable estimations, quantitative models of treatment processes will also be needed.

The use of chemical compounds for the disinfection of drinking water appears to introduce a new category of risks. Chlorine compounds and ozone have the ability to react with organic residues in the water, thereby producing toxic substances (DBP), possibly even with carcinogenic properties. This may lead to a situation where the manager or designer of a drinking water production plant has to balance two conflicting interests. Addition of extra disinfectant decreases the risk of infectious diseases, but increases the risk caused by DBP at the same time. A decrease in chemical disinfectant increases the risk of pathogenic organisms. The application of quantitative risk assessment for both unwanted effects offers the opportunity to balance these risks. It is even conceivable that there is an optimum where the combined health risk is at a minimum (fig. 5.1).

In addition to offering a rational basis for judging drinking water safety and the design of drinking water production plants, quantitative risk assessment may play a part in balancing of different interests on a management level. However, weighing risks of a different nature necessitates the use of a generally valid measure for the effects of pathogenic organisms in the environment. Some alternatives for such a measure are listed in 6.2. Contrary to common practice for chemical substances, the expected number of fatalities is not a very suitable measure. The most common consequence of infection is a number of days of illness, sometimes followed by chronic symptoms or permanent invalidity. Measures that take this into account, like the loss of Quality Adjusted Life Years (QALY's), are better suited than the loss of life expectancy proper. Politi-

cians may also be forced to make choices based on the economic burden of the presence of certain microorganisms. The larger the differences between effects, the greater the need for social research into risk perception among the public. The risk of acute gastroenteritis after exposure to a virus will probably be perceived quite different from the risk of cancer after exposure to chemical substances, like DBP's. An important aspect in this latter example is the long latency for the development of cancer, prohibiting direct notice or control of the experienced risk.

This first survey of quantitative risk analysis has led to a lot of questions to be investigated. The reliability of the risk estimate depends on the quality of the dose-response data and the goodness of fit of the mathematical model. Dose-response experiments with human volunteers are probably not feasible in the Netherlands. Animal experiments may offer more insight into the fundamental problem of how the dose-response relation changes with weakened immune response (4.3). Better understanding of these changes is necessary if risk analysis is to be extended to subpopulations with different immune competence.

Collection of reliable exposure data is equally important. To mention a few: better understanding of the efficiency of detection methods, determination of the fraction of organisms viable to cause infection, distribution of the unboiled water consumption among the population of the Netherlands, and the removal efficiency of water treatment processes (see 3.5).

Finally, there is also need to know more about public acceptance and perception of microbial health risks: which measure reflects best the consequences of infection (illness, death), and how should the risks of pathogenic microorganisms and chemical compounds be balanced?

Now that the methodology for quantitative estimation of health risks seems to enter the stage of practical usefulness, the need for government guidelines, based on health risks, increases. With the help of quantitative risk assessment the risk for public health of exposure to pathogenic microorganisms may be treated the same way as the risks of substances or accidents. A general guideline for what constitutes an acceptable health risk, and what does not, accommodates the needs of drinking water managers, and conforms to already existing practice.

Samenvatting

Het nederlandse drinkwater geldt als veilig voor de consument. Het systeem voor kwaliteitsbewaking van drinkwater is gebaseerd op maximumconcentraties voor verschillende parameters. In het geval van micro-organismen zijn de belangrijkste normen die voor indicatoren voor faecale verontreiniging. Hierbij gaat men ervan uit dat pathogene micro-organismen gewoonlijk van faecale oorsprong zijn.
Door verschillende recente ontwikkelingen is deze bewakingspraktijk onder druk komen te staan. Epidemieën van aan drinkwater gerelateerde ziekteverwekkers zijn voorgekomen op plaatsen waar het drinkwater voldeed aan de geldende microbiologische normen (Melnick and Gerba, 1979; Craun, 1981; Lippy and Waltrip, 1984; O'Neil et al., 1985). De huidige kwaliteitsstandaard voorziet ook niet in de controle op opportunistische ziekteverwekkers, microbiële toxinen of allergenen, etc. Bovendien kan de correlatie tussen het voorkomen van pathogene organismen en indicatororganismen niet aanwezig zijn, vooral als het gaat om "nieuwe" pathogenen, zoals *Cryptosporidium.* Dit organisme is bovendien beter bestand tegen waterzuiveringsmaatregelen, zoals chemische desinfectie.
Veel pathogene organismen kunnen tegenwoordig direct aangetoond worden, zodat men in plaats van indicator-organismen meteen naar ziekteverwekkers kan zoeken. Daarnaast is er, vooral in de Verenigde Staten, een ontwikkeling op gang gekomen waarbij men gezondheidsrisico's tracht te voorspellen met behulp van dosis-effectmodellering.
Voor een aantal bekende ziekteverwekkers zijn, soms al sinds tientallen jaren, dosis-respons-experimenten gedaan, op menselijke vrijwilligers. Hierbij stelt men proefpersonen bloot aan een aantal verschillende concentraties van een (pathogeen) micro-organisme, en bepaalt hoeveel mensen geïnfecteerd worden als functie van de hoeveelheid toegediende pathogene organismen (kiemen, viruseenheden, (oo)cysten). Deze experimenten zijn verricht bij concentraties waarbij effecten als infectie, of bepaalde (milde) symptomen van ziekte voldoende vaak voorkomen, teneinde het aantal benodigde proefpersonen bij deze kostbare experimenten zoveel mogelijk te beperken.
De concentraties waarin deze organismen in het drinkwater voorkomen zijn vele ordes van grootte lager. Als men de resultaten uit deze laboratoriumexperimenten wil gebruiken voor het voorspellen van de kans op infectie bij deze zeer lage concentraties, moet men dus extrapoleren. Hiervoor kan een mathematisch model gebruikt worden. Zo'n model kan men opstellen door bepaalde zeer algemene aannames te doen over het proces van infectie, en deze in een mathematische functie te vertalen. In dit rapport worden enkele van deze modellen geïntroduceerd (hoofdstuk 4). Als een model goed "past" op de experimentele gegevens, wordt het geaccepteerd voor risicoschatting.
Voor zeer lage doses, zoals die in het algemeen voorkomen in drinkwater, zal de kans op

infectie ook klein zijn. Te klein om deze direct te bepalen in een experiment. Het model biedt nu de mogelijkheid om ook voor deze zeer lage doses een schatting te doen van het gezondheidsrisico. Een eigenschap van de gebruikte modellen is de afwezigheid van een drempelwaarde: bij afname van de dosis is er een gestage afname van de kans op infectie, maar hoe klein de (gemiddelde) dosis ook is, er is steeds een eindige kans op infectie. Gezien de goede overeenstemming met experimentele gegevens kan de mogelijkheid, dat één enkel micro-organisme infectie veroorzaakt bij tenminste een deel van de blootgestelde populatie, niet worden uitgesloten.
Als er overeenstemming bestaat over het maximaal acceptabel gezondheidsrisico voor een bepaald pathogeen organisme, dan kan men de dosis-effectrelatie gebruiken om dit risiconiveau te vertalen naar een maximaal toegestane concentratie in het drinkwater.
Vooralsnog is er in Nederland geen richtlijn voor een dergelijk acceptabel gezondheidsrisico, dan wel maximum toelaatbaar gezondheidsrisico. Het door de USEPA gehanteerde niveau van 10^{-4} voor de individuele kans op infectie per jaar is mogelijk bruikbaar. Gebruik makend van de schaarse gegevens die beschikbaar zijn leidt deze aanname tot kansen op sterfte tengevolge van blootstelling aan pathogene micro-organismen die redelijk overeenstemmen met de normen zoals die gehanteerd worden voor gevaarlijke stoffen (VROM, 1989). Voor verschillende organismen is de variatie echter aanzienlijk, zie tabel 5.1 en hoofdstuk 5.1.5.
Aangezien infectie voorafgaat aan ziekte en eventueel sterfte, kan men de kans op infectie hanteren als een vorm van "worst case". Uitgaande van deze normwaarde van 10^{-4} voor de individuele jaarlijkse kans op infectie kan men nu voor verschillende organismen maximaal toelaatbare concentraties in drinkwater berekenen.
Voor vele organismen blijkt de kans op infectie per ingenomen organisme (zie 5.1.1, de lineaire benadering bij lage doses) zo groot te zijn, dat de daaruit geschatte maximumconcentraties ver beneden de laagst meetbare waarde liggen. Voor *Cryptosporidium* zouden 500 monsters van ieder 2000 liter nodig zijn om een enigszins betrouwbare schatting van de toelaatbare concentratie (7×10^{-6} per liter) te maken (Regli et al., 1991). Daarom zal een bewakingsprogramma moeten worden uitgevoerd op basis van het ruwe, ongezuiverde water. De concentraties in het drinkwater moeten vervolgens berekend worden, met inachtname van een (geschatte) efficientie van het zuiveringsproces in kwestie. Om deze schatting betrouwbaar te kunnen uitvoeren moeten voor zuiveringsprocessen eveneens kwantitatieve modellen opgesteld worden.
Het gebruik van chemische stoffen voor de desinfectie van drinkwater blijkt een andere categorie van risico's met zich mee te brengen. Chloorverbindingen en ozon kunnen chemisch reageren met organische verbindingen in het water, waardoor toxische verbindingen kunnen ontstaan (DBP), mogelijk met carcinogene werking. Dit leidt tot een situatie waarbij de toezichthouder of ontwerper van een drinkwaterbereidingsinstallatie twee tegenstrijdige belangen tegen elkaar moet afwegen. Toevoegen van extra desinfectans verlaagt het risico op infectieziekten, maar verhoogt het risico ten gevolge van DBP's. Verminderen van chemische desinfectie verhoogt weer het risico van pathogene micro-organismen. Door nu voor beide ongewenste verschijnselen een kwantitatieve risico-analyse op te stellen, kan men beide risico's tegen elkaar afwegen. Het is zelfs niet ondenkbaar dat er een optimum gevonden kan worden waarbij het totale gezondheidsrisico minimaal is (figuur 5.1).
Naast het verschaffen van een rationele basis voor het beoordelen van de veiligheid van drinkwater, en het ontwerpen van installaties voor drinkwaterbereiding, kan kwan-

titatieve risico-analyse een rol spelen bij de afweging van verschillende belangen op beleidsniveau. De afweging van ongelijksoortige risico's maakt echter wel het gebruik van een algemeen geldige maat voor de gevolgen van pathogene organismen in het milieu noodzakelijk. Hiervoor bestaat een aantal alternatieven, opgesomd in 6.2. Anders dan gebruikelijk voor bij voorbeeld chemische verbindingen, is het te verwachten aantal sterftegevallen een niet erg geschikte maat voor de gevolgen. Meest voorkomend gevolg van een infectie is immers een aantal dagen ziekte, soms gevolgd door chronische verschijnselen of invaliditeit. Grootheden die hiermee rekening houden, zoals verlies aan Quality Adjusted Life Years (QALY's) , zijn dan ook meer geschikt dan enkel het verlies aan levensverwachting. Politici en beleidsmakers kunnen bovendien genoodzaakt zijn afwegingen te maken die gebaseerd zijn op de economische kosten van het voorkomen van bepaalde micro-organismen. Naarmate gevolgen met elkaar moeten worden vergeleken die verder uiteen liggen, is de noodzaak van sociologisch onderzoek naar de perceptie van risico's groter. Het risico van acute gastro-enteritis na blootstelling aan een virus zal bij voorbeeld heel anders gewaardeerd worden dan het risico op kanker na blootstelling aan chemische stoffen, zoals DBP's. Een grote rol hierbij speelt ook de grote latentietijd die in het laatste geval kan bestaan, zodat het oorzakelijke verband niet meer direct waargenomen of beïnvloed kan worden.
Deze eerste verkenning van de kwantitatieve risico-analyse heeft tevens vele onderzoeksvragen aan het licht gebracht. De betrouwbaarheid van de risicoschatting hangt af van de kwaliteit van de dosis-responsgegevens en de mate waarin het model hierop past. Dosis-responsexperimenten met menselijke vrijwilligers zijn in Nederland waarschijnlijk niet haalbaar. Experimenten met proefdieren kunnen echter wellicht wel meer inzicht geven in de fundamentele vraag hoe de dosis-responsrelatie verandert bij verzwakking van de de immuunrespons (zie 4.3). Een beter begrip hiervan is cruciaal als men bij risico-analyse ook rekening wil houden met verschillen in vatbaarheid tussen bevolkingsgroepen. Even belangrijk is het verzamelen van betrouwbare gegevens over blootstelling. Om er enkele te noemen: een beter begrip van de efficientie van detectiemethodes, methodes voor bepaling van het percentage infectieuze organismen, verdeling van de consumptie van ongekookt water voor de nederlandse bevolking, de efficientie van waterzuiveringsprocessen. Zie hiervoor ook 3.5. Tenslotte is er ook behoefte aan meer kennis over de publieke acceptatie en de perceptie van microbiële gezondheidsrisico's: welke maat voor de gevolgen van infectie (ziekte, sterfte) geeft de ernst ervan het beste weer, hoe moeten risico's van pathogene micro-organismen en die van chemische verbindingen tegen elkaar worden afgewogen?
Nu de methodologie voor het kwantitatief afschatten van gezondheidsrisico's praktisch bruikbaar lijkt te worden, neemt de behoefte aan overheidsrichtlijnen, gebaseerd op gezondheidsrisico's, toe. Met behulp van kwantitatieve risico-analyse is het mogelijk om het risico voor de volksgezondheid van de blootstelling aan pathogene micro-organismen net zo te behandelen als de risico's van stoffen en calamiteiten. Een algemene richtlijn voor wat een aanvaardbaar gezondheidsrisico is en wat niet, komt tegemoet aan een behoefte bij drinkwaterbeheerders, en speelt in op een in feite al bestaande praktijk.

Introduction

The classical approach to drinking water safety consists of monitoring the end product. Most tests are performed on the drinking water as it leaves the treatment works, some testing is also done on water within the distribution network as it is received by the end user, the consumer.
Since microbial contamination originates mainly from (human) faecal sources, bacterial monitoring usually includes total coliforms, faecal coliforms, and faecal streptococci, at least from a classical point of view (Havelaar, 1983; Waterleidingbesluit, 1984; AWWA, 1993; Geldreich, 1990). The presence of these faecal indicator organisms is assumed to correlate with the presence of microbial pathogens. Indicators of faecal contamination are widely used because of their easy detection and relative abundance, facilitating quantitative and rapid assays.
Testing for faecal indicators may convey a false sense of safety, however, because their concentrations are only indicative for concentrations of pathogenic organisms insofar as they occur together in polluted sources. In addition to this, faecal indicators and pathogenic organisms should share the same characteristics: equally resistant to water treatment and disinfection, and similar physico-chemical properties. Ideally, the positive correlation between a presumed indicator and the corresponding pathogenic organisms must be ascertained for every pathogenic organism, in every situation.
In recent years this approach to drinking water safety has become subject to increasing criticism. Monitoring for coliform bacteria, turbidity, and disinfectant residuals has been demonstrated insufficient for the prevention of waterborne outbreaks (Payment et al., 1993)). Today's standard quality procedures also do not include indicators for opportunistic pathogens, microbial toxins, or allergens, etc. .
Waterborne outbreaks have been documented in regions where the drinking water quality met with existing microbiological criteria (Melnick and Gerba, 1979; Craun, 1981; Lippy and Waltrip, 1984; O'Neil et al., 1985). Therefore, low-level transmission of waterborne disease must be assumed to occur. At the same time, outbreaks probably constitute a small fraction among a large number unnoticed events: the proverbial "tip of the iceberg".
The presumed close correlation between pathogen occurrence and the detection of indicator organisms may not always be present, especially in the case of relatively "new" pathogens, like the protozoan *Cryptosporidium*. Protozoan (oo)cysts and enteric viruses are more resistant to physicochemical treatment and disinfection than most indicator organisms. Fortunately enough, methods for direct detection of various pathogens are often available today, thereby providing an alternative to the indirect methods mentioned above.
The increased sensitivity of microbial detection methods has led health researchers to

develop an increased awareness of the magnitude of infectious doses for the pathogens under consideration. For some of the major pathogens dose-response information is available. Stochastic models fitting these data indicate that the probability of infection after ingestion of a single infectious unit or particle (Furumoto and Mickey, 1967; Haas, 1983) may not be neglected. In other words: the concept of a minimal infective dose may convey a false sense of safety, because the entrance of a single infectious unit already implicates a nonzero probability of infection. And when infection does occur, this may lead to the development of symptoms of illness within the host, in some cases ending in death, also with a nonzero probability (Armitage et al., 1965; Haas, 1983).
This new view upon microbial infection as a non-threshold phenomenon presents governments and water quality managers with the notion that there is no such thing as a concentration threshold for microbial safety, below which no risk whatsoever exists for any individual in the whole population. Hence, modern safety regulations and legislature have to be based upon the definition of tolerance levels, based in turn upon publicly acknowledged risk limits.
The Dutch National Environmental Policy Plan (VROM, 1989) provides a list of objectives for the risk assessment approach. Provide risk guidelines for different agents: how is a health risk defined, and how should it be measured and which are the major groups of agents or organisms that impose risks on the public. Set standards within groups of agents: which end effects are taken into consideration, and how are these translated into risk limits. Set priorities: which are the major substances or pathogenic organisms, and which subpopulations should be protected, and to what extent. Assess costs of risk reduction and evaluate the effectiveness of preventive measures. Forecast future developments: use knowledge about present risk sources to make assumptions about the impact of emerging pathogenic organisms, for instance. Unify assessment procedures so as to enable relative weighing of different risk estimates: when the effects of microbial contamination of drinking water and the effects of chemical contamination with byproducts of disinfectants are expressed on the same scale, their combined effect may be minimized.
This preliminary survey will focus primarily on the assessment of risk from pathogenic microorganisms in drinking water. Various sources of uncertainty will be identified. In addition to uncertainties in the dose-response parameters, these include the shape of the frequency distribution for the occurrence of the microorganisms in the drinking water, and spatiotemporal variations of this distribution. At a later stage, the analysis may be extended to specified risk groups, eventually with specific consumption patterns. Additional information will also be required to assess the relationship between the occurrence of organisms in the raw and treated (finished) water. The requirements for this analysis are briefly summed up. Some reference will be given to the factors determining the public decision process, which are necessary for setting risk limits for environmental hazards.
The final goal of the study, of which this survey is the first part, is the establishment of a framework for risk analysis, equivalent to the methods that are in use for risk assessment of contamination with chemical substances. We hope to finally arrive at some concept of combined risk analysis: weighing microbiological hazards versus toxicological hazards. The approach aims at minimization of the combined risk of microbiological and chemical hazards an individual is exposed to as a result of drinking water consumption.

Various problems and issues that may occur in risk assessment practice are illustrated with excerpts from an example: a case of possible protozoan contamination of drinking water from a conventional surface water treatment plant. These quotations are reproduced in small print (sans-serif) so that they may be easily recognized within the main text.

Chapter 1

General framework

1.1 Quantitative Risk Assessment: definitions

Prior to any quantitative considerations, the basic concepts of risk must be defined. From the FAO/WHO food standards programme on *risk analysis* (FAO/WHO, 1993):

> Risk can be defined as the potential for the occurrence of unwanted negative consequences of an event. The elements of risk are: a choice of action or loss (voluntary, involuntary), a chance of loss (probability, frequency), and a magnitude of loss (character, extent, timing).

The Dutch National Environmental Policy Plan (1989) states, somewhat more explicitly:

> Risk is defined as the unwanted consequences of a particular activity in relation to the likelihood[1] that this may occur.

with additional specifications:

> The individual risk is the likelihood that a person will suffer a given detrimental effect as a result of exposure to an agent (expressed in probability units per year or related to an average concentration per year).
>
> Group risk is the likelihood per year that a group of at least a certain size will all be the victim of a single accident (event, contamination) at one and the same time.
>
> A risk group is a section of the population that has been selected as having an increased risk in relation to a specific source or agent.

Within the original context, an "agent" primarily designates a chemical substance. Without modifications, these definitions may be used for microbial agents just as well. Finally, the risk for ecosystems is defined:

[1] The *Probability* of an event may be measured by the ratio of the number of possible favourable occurrences to the number of all possible occurrences. Note that the event needs not yet have taken place. When an event has taken place, each possible outcome may have occurred with a certain *Likelihood*

> The collective risk for ecosystems is the likelihood per year that an ecosystem will suffer a particular deleterious effect as a result of exposure to an agent.

This category is of less acute importance to the present project, although in principle it may be applied for microbial sources just as well as for chemical substances (recent outbreak of viral disease among seals in the North Sea, but also future developments regarding the release of genetically modified microorganisms into the environment).

1.2 Quantitative Risk Assessment: procedure

Any quantitative approach to risk analysis starts with a survey of potential causative agents of health damage. These potential hazards must be identified to such an extent that research concerning occurrence, mode of action, and health effects is possible. Important characteristics include the degree of exposure (concentration of the pathogen), duration and frequency of the exposure, characteristics of the pathogen, size of the exposed area/population, and nature of the detrimental effect.
When a list of potentially detrimental effects has been made for each selected agent, the likelihood of their occurrence must be estimated. Standard procedure consists of obtaining dose-response data, and using a mathematical model (be it empirical or based on physiological knowledge about underlying mechanisms) to extrapolate to the very low doses, occurring under normal circumstances. This is the actual risk assessment procedure (see the upper part of fig. 1.1). In the case of microbial health risks, the causal chain leading from contact with a pathogen on to end effects like illness or death, is usually not known, at least not well enough to allow reliable quantitative modelling. Therefore, our first objective consists of quantitative estimation of the risk of infection, the initial stage of this chain of possible events. Point estimates of the risks for more advanced end effects will have to be obtained mostly from epidemiological evidence, since experimental data will be very hard to come by.
As soon as quantitative risk estimates are available, the acceptability of these risks enters the discussion.
Quantitative risk assessment may be utilized to translate environmental occurrence of pathogens to health risks. Conversely, as soon as risk limits have been set, these can be converted into pathogen concentrations. When our knowledge of dose-response relations for pathogenic organisms increases, risks from different organisms can be weighed against each other. This may be useful for the design of treatment procedures in a drinking water production plant, for water quality monitoring programs, etc.

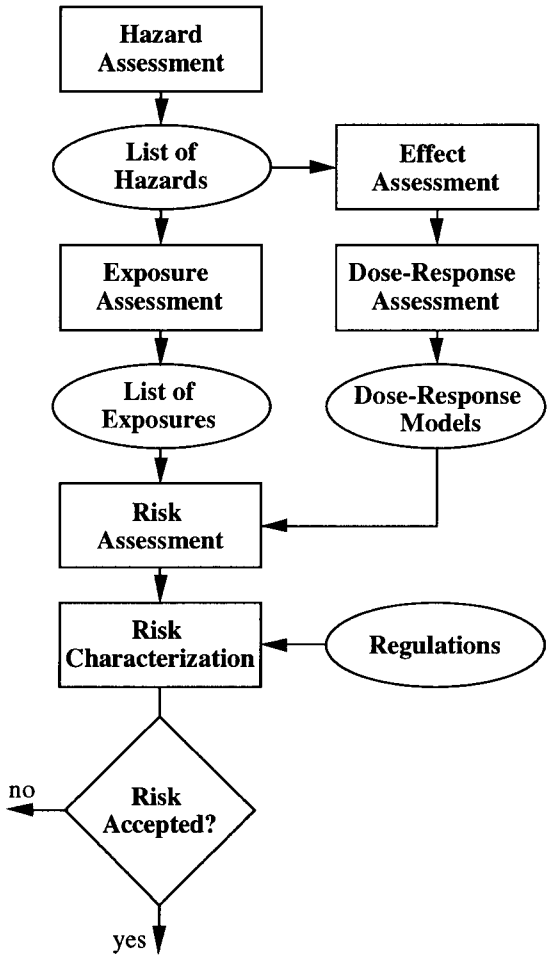

Figure 1.1: Risk assessment procedure. When a list of hazards has been compiled, two actions must be undertaken for each of these hazards: find a dose-response relation, and estimate the dose an individual person is exposed to. From these data the amount of risk an individual person may experience, can be calculated. This is called risk characterization. The acceptability of this risk level can be checked against existing regulations. When the limiting value for acceptability is exceeded, preventive action must be taken. In case the risk levels should be far below this limit, it is conceivable that the measures against microbial contamination are relaxed. Considerations like this belong to the field of risk management.

Chapter 2

Hazards

With regard to quantitative risk assessment, we will define hazards as the sources of any negative health effect. This includes exposure to a pathogenic microorganism or a chemical substance. In HACCP practice (section 5.2.1), the actions leading to such exposures are usually considered the hazards. Therefore, in HACCP a hazard may involve more than one pathogenic microorganism or chemical substance.
As far as pathogenic microorganism species are concerned, hazards may be of bacteriological, viral, and protozoological origin. In addition to this, growth of some organisms may cause the release of toxic substances (table 2.1).
Microbial contaminants in drinking water are often subdivided into three categories: *pathogenic organisms* (causing infectious disease in both healthy and compromised individuals), *opportunistically pathogenic organisms* (causing disease only when environmental factors or the condition of the host promote this), and *nonpathogenic organisms* (do not cause disease). In many cases, distinction between these categories is not clear. Mechanisms of pathogenicity are not well known, especially for opportunistically pathogenic organisms.
Actions that introduce microbiological hazards into the drinking water production process are (Havelaar, 1994): faecal pollution of raw water sources and growth of pathogenic organisms in the source water or the treated water (bacteria, toxigenic algae, free-living protozoans), enhanced by factors like thermal pollution and/or eutrophication. Pollution may also occur in drinking water storage facilities, or in the distribution network, as a result of various human activities. Design flaws may cause back-siphonage,

(group of) organisms	effect
enteric bacteria	gastroenteritis
Legionella pneumophila	fatal pneumonia
hepatitis virus A and E	hepatitis
Coxsackie virus	cardiomyopathies
Cryptosporidium parvum	gastroenteritis
Giardia lamblia	gastroenteritis
blue-green algae	neurotoxic effects

Table 2.1: Some of the pathogenic organisms associated with drinking water, and the effects they may cause upon infection, to illustrate the diversity of hazards that may occur (AWWA, 1993)

Disease:	USA, 1971-1988		UK, 1937-1986		Sweden, 1975-1984	
	outbreaks	cases	outbreaks	cases	outbreaks	cases
Gastroenteritis (unknown etiology)	279	64965	8	4543	19	6330
Giardiasis	103	25834	1	108	1	56
Chemical poisoning	55	3877	4	531		
Shigellosis	40	8806	4	5088	2	40
Viral gastroenteritis	26	11799			1	3200
Hepatitis A	23	737			1	33
Salmonellosis	12	2370			2	4
Campylobacteriosis	12	5233	5	919	5	3120
Typhoid fever	5	282	8	217		
Yersiniosis	2	103				
Cryptosporidiosis	2	13117	2	66		
Chronic gastroenteritis	1	72				
Toxigenic *E. coli*	1	1000			1	100
Cholera	1	17				
Dermatitis	1	31				
Amebiasis	1	4	1	17		
Streptobacillary fever			1	304		
Aeromonas					1	10
total	564	138247	34	11794	32	11847

Table 2.2: Waterborne disease outbreaks in the USA, UK, and Sweden (Andersson and Stenstrøm, 1986; Galbraith et al., 1987; Craun, 1991).

maintenance deficiencies may result in leaks and pressure drops, etc.

2.1 Hazardous microorganisms

A list of pathogenic microorganisms that are most important for public health may be inferred from epidemiological data. Additional information about possible candidate organisms may be obtained from laboratory studies.

Epidemiological data are collected for outbreaks related to different exposure pathways. Most relevant are those directly related to the consumption of contaminated drinking water. A list of recent outbreaks of waterborne disease in the USA, Great Britain, and Sweden is reproduced here in table 2.2, to illustrate the significance of the best known pathogens for public health. Note the large fraction of outbreaks of gastroenteritis that cannot be attributed to a specific pathogen.

The protozoan *Cryptosporidium*, for instance, has only been recently acknowledged as a significant pathogen for humans. As detection methods continue to improve, the number of cases with unknown etiology may decrease further.

Pathogenic microorganisms that cause outbreaks in relation with recreational waters or shellfish consumption may also be relevant for drinking water related health risks. And finally, the study of foodborne or zoonotic outbreaks may also provide information on the pathogenic potential of microorganisms, and assist in the decision whether an organism should be regarded a health hazard.

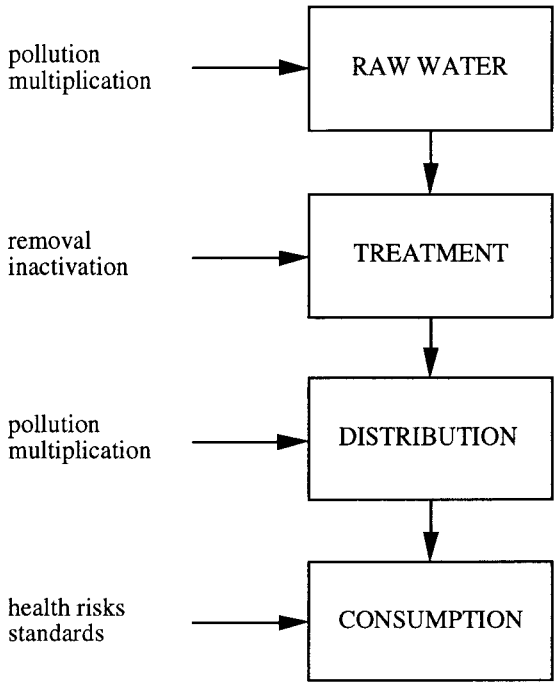

Figure 2.1: Areas of interest for the assessment of health risk in a drinking water production plant

2.2 Hazardous activities and/or situations

Along the chain of drinking water production: intake of source water, treatment, storage and distribution, different hazards must be considered (figure 2.1). A non exhaustive list, ordered by position within the production process is given below.

Ground water sources are subject to contamination via transport of matter in different soil layers. Leakage from sewage pipes, or land application of sludge, for example, may introduce pathogenic organisms into the subsurface. Due to fast die-off of bacteria in soil, viruses and protozoa are considered the main hazards for the use of ground water. Of these two, viruses may be most important, because their small size allows them to travel large distances in a relatively short time, see section 3.1.3.

Surface water sources The predominant sources of microbial contamination of raw surface waters are human and animal faeces. Human faecal input may originate from direct contact (recreation, workers), or from sewage or septage (effluents, sludges). Animal input results from direct exposure to wild animals, manures, and surface run-off. When pathogenic organisms from these sources are able to reach an intake site of a drinking water production plant, they represent a health hazard. This may be true for viruses, bacteria, and protozoan (oo)cysts. To avoid unnecessary measurement efforts, model descriptions based on comprehensive databases of water transport systems, faecal inputs from different sources, and output volumes to drinking water production sites must be developed.

Water treatment A large number of methods is in use for the removal of pathogens and other undesired substances from source waters. Usually, two or more methods are used in cascade, to achieve a satisfactory reduction of pathogen numbers. The performance of a given method depends upon the process properties, but environmental parameters like temperature, and the input load may also influence the decontamination efficiency. Apart from intake of contaminated water, hazards occurring in drinking water production facilities include various causes for process failure. These are reviewed elsewhere (Havelaar, 1994).

Storage and distribution Hazards introduced after the finished water leaves the production site : recontamination, due to structural or procedural flaws, and/or regrowth of microorganisms. Distribution systems may be accidentally contaminated by pressure-drops, back-siphonage, construction and repair works, etc. Certain bacteria may multiply in the distribution system or in the plumbing systems inside buildings, thereby representing new health hazards that cannot be prevented directly by appropriate treatment.

The source load with microbial pathogens for both surface waters and ground water sources is subject to a prospective investigation, currently underway in our laboratory.

2.3 Disinfection By-Products

Since the mid-1970's, awareness has increased that chemical disinfectants (chlorine, chloramines, ozone, and chlorine dioxide) cause an increase in concentration of various undesired substances. The most important of these disinfection by-products (DBP) are:

Trihalomethanes (THM) chloroform, dichlorobromomethane, dibromochloromethane, bromoform.

Haloacetic acids di- and trichloroacetic acids.

Chlorinated aldehydes and ketones, chloropicrin, and many other compounds (in minor amounts).

Bromate and aldehydes formaldehyde, acetaldehyde.

THM may be used as indicators, because they constitute a major fraction of the total DBP. The drinking water producers are using a maximum acceptable concentration (MAC) of 0.2 mg/l for active chlorine (with limit value for short term increases of 1 mg/l). The acceptable level of THM resulting from residual chlorine is set at 0.55 μmol/l, equivalent to 70 μg/l chloroform (VEWIN, 1985). In a more recent publication, KIWA has proposed detailed guidelines for updated regulations on the subject of microbial safety and disinfection by-products (van Dijk-Looijaard, 1993). A table summarizing the latter proposals is reproduced here (table 2.3). The U.S. Environmental Protection Agency enforces a Maximum Contaminant Level (MCL) of 10ppm (0.10 mg/l) for total THM.
The availability of risk assessment procedures for similar noxious substances will enable comparison between, or even balancing (section 5.1.7) of the effects of microbial contamination and the effects of by-products originating from chemical countermeasures.

Parameter[1]	Standard (μg/l)	Measuring Frequency[5]	Remark
chloroform	5	3-monthly[4]	2
bromoform	5	3-monthly[4]	2
bromodichloromethane	6	3-monthly[4]	2
chlorodibromomethane	5	3-monthly[4]	2
chlorite	200	3-monthly[4]	2
trichloroacetic acid	100	3-monthly[4]	2
bromate	0.5	3-monthly[4]	2
chlorate	-	3-monthly	7
chlorine	5000	daily	3
ozone	-	daily	3
hydrogen peroxyde	-	daily	3
chlorine dioxyde	-[6]	daily	3
chloramine	3000	daily	3
cyanogen chloride	70	yearly	2
dibromoacetonitril	100	yearly	2
dichloroacetonitril	90	yearly	2
dichloroacetic acid	50	yearly	2
formaldehyde	90	yearly	2
trichloroacetonitril	1	yearly	2
chloral hydrate	10	yearly	2

1. When present in the untreated water, measurement is obligatory.
2. Measurement only obligatory when formation of these compounds with the applied disinfection method is possible.
3. Only when this disinfectant is used.
4. In case of any change in disinfectant and raw water source, the sampling frequency must be adjusted.
5. When measured concentrations stay below the standard value, or remain stable during an entire one year period, a lower sampling frequency may be applied in consultation with the Health authorities.
6. related to the amount of chlorite formed when chlorine dioxide is used.
7. For surface water treatment and/or when chlorine is used.

Table 2.3: Some Disinfection By-Products and the proposed maximum acceptable concentrations (van Dijk-Looijaard, 1993).

2.4 Research needs

Information about microbial hazards usually comes from waterborne outbreaks. In as little as 50% of all recent waterborne outbreaks in the USA, the causative agent has been identified. Partially, this is due to the fact that an outbreak is usually identified as such when it is well underway. The establishment of a reliable and temporally dense microbiological monitoring system may improve the probability to predict waterborne outbreaks, or at least give an early warning signal when the risk increases substantially. Nevertheless, the occurrence of hitherto unknown pathogens can never be excluded *a priori*, see *Cryptosporidium* as a relatively new species of pathogenic importance. Research needed to improve hazard assessment:

- Set up a database to identify, characterize, and list all of the microbes in drinking water that are potential agents of disease, and identify and characterize the currently unidentified agents associated with documented chronic or acute illness transmitted via drinking water.

And, with respect to Desinfection By-Products (DBP), research is needed to:

- develop an accurate, coordinated data base on the occurrence of contaminants in drinking water, as well as air, food, and other media (including chemicals and microbials).
- understand the mechanisms by which chemical contaminants in drinking water are absorbed, distributed, metabolized, and eliminated from the human body, so as to develop more accurate physiologically based models of these phenomena.
- understand the mechanisms by which these agents cause toxic effects and the variations in these responses from test animals to humans.
- develop new approaches to the study of complex mixtures such as those found in drinking water, especially to determine the prospects for synergistic or antagonistic interactions that may affect the shape of the dose-response relationship of the individual chemicals, and to examine noncancer end points.

Chapter 3

Exposure assessment

The received dose, i.e. the amount of pathogenic microorganisms an individual person is exposed to per unit time, must be estimated from the following quantities:

- The concentration of pathogenic organisms in a drinking water sample
- The fraction of these organisms that is capable of initiating infection
- The amount of unheated water that has been swallowed

3.1 Estimation of the concentration of organisms

The concentration of pathogenic microorganisms in the drinking water may be determined via one of the following strategies:

- Direct measurements
- Estimation via the use of index organisms
- Inference from concentrations in source waters and log reduction rates of treatment operations

3.1.1 Direct measurement

Direct measurements of the concentration of pathogenic microorganisms in finished water are usually not feasible. Although the sensitivity of detection methods has increased over the past years, concentrations in the drinking water at the consumer level are (and, for that matter, *should be*) typically below those at which reliable estimation of concentrations is possible. This, however, does not necessarily lead to the conclusion that such a water is safe for drinking. Preliminary work on the setting of exposure limits based on quantitative risk assessment indicates that acceptable risk levels correspond to concentrations less than a few organisms per million litres of drinking water. For *Cryptosporidium* 500 samples of 2000 liters each would be needed to make a reasonably accurate estimation of the allowed concentration (7×10^{-6} per liter) (Regli et al., 1991). Therefore, alternative strategies are needed to estimate the pathogen concentration.

Pathogens (direct detection) in raw water, to establish treatment criteria in different stages of treatment, to assure proper performance exceptionally in end-product or in distribution water
Escherichia coli by direct methods: replaces thermotolerant coliforms in all stages of production and distribution
Coliform bacteria in piped, treated supplies, for early warning
Faecal streptococci additionally in important stages of treatment and distribution
Bacteriophages F-specific RNA-phages in all stages of treatment *Bacteroides*-phages additionally in raw waters
Spores of sulphite-reducing clostridia in all stages of treatment presumed valid indicator for protozoan (oo)cysts
Heterotrophic plate-counts, Biofilm potential will be replaced by AOC-measurements (Assimilable Organic Carbon) and *Aeromonas*

Table 3.1: Categories of organisms for microbiological monitoring of drinking water.

3.1.2 Estimation using index organisms

Index organisms are easy to detect, like indicator organisms, but their concentrations are assumed to be proportional to those of (a class of) pathogenic organisms. In table 3.1, the main categories are listed, together with their significance for monitoring purposes. The application of index organisms for the estimation of health hazards depends upon the existence of a good correlation between the (considered class of) pathogens and the indicator organism in question. Such a correlation has not been established in all cases, certainly not in a quantitative sense. Good detectability and/or relative abundance of indicator organisms promotes their being used also when there is only a loose relationship with the occurrence of the actual pathogen. On the other hand, the detection of this latter organism may be very difficult or expensive to perform.

3.1.3 Indirect estimation

Indirect estimation of pathogen concentrations from source water levels and reduction rates relies on the opportunities for estimating the latter. There are two different situations to consider: production of drinking water from contaminated surface waters in a treatment plant, or natural disinfection of ground water.
The pathogen concentrations in source water may be several log-units higher than in finished water. Therefore, detection at this stage of the production process is a lot easier, and probably more accurate. Higher concentrations provide a better opportunity to estimate mean levels and, if possible, obtain some knowledge on the frequency distribution for the pathogenic microorganisms. The critical point with this approach, is that in addition to raw water concentrations, the efficiency with which the organism in question is removed in the treatment process, must be known. For some organisms information on log-reduction rates is available, but little is known about the accuracy of these numbers. In particular, this information is based on lab or pilot scale experiments.

The errors introduced by extrapolation to full scale treatment facilities may be difficult to control.
Additional information is needed to estimate efficiencies of combinations of different treatment steps, or even perform an uncertainty analysis. If we had enough data to fit a frequency distribution for the reduction rate, instead of a point estimate, this could be used to construct a confidence region for the estimated pathogen concentration. Another, more comprehensive approach, may be to set up physico-chemical models for treatment steps of concern. These may be combined into treatment plant models. Raw water occurrence data may then be fed into such a model, to obtain a prediction of the occurrence of pathogenic organisms in the finished water.
A special case that has to be considered, is that of the estimation of pathogen concentrations in ground water. Passage of water through soil layers may be considered a process of natural disinfection. Extremely high reduction rates are possible, depending upon the dimensions and the properties of the soil (van Olphen et al., 1993). The increase in input of (not only) microbiologically contaminated waters gives rise to concern about the limitiations of this natural disinfection process. On one hand, the ever increasing demand of drinking water leads to water shortage. When too much water is extracted from a well, ground water levels will decrease, leading to environmental damage. On the other hand, injection of contaminated water into ground water stores, be it on purpose (river bank infiltration), or by accident (leakage or seepage, for instance from sewage lines), may contaminate nearby wells.
Viruses and protozoa are considered the main hazards for the use of ground water. Of these two, viruses may be most important, because their small size allows them to travel large distances in a relatively short time. Measurements of virus transport in model systems indicate a large variability in transport velocity, especially when there are microfissures which constitute preferent paths for these organisms (Bales et al., 1989). Physico-chemical models for virus transport in different soil layers have been developed, with refinements continually going on (Kinoshita et al., 1993; McKay et al., 1993; Bales et al., 1993). Important parameters are the hydrological residence time, moisture content, and temperature profiles (Hurst, 1991)

3.1.4 Recovery of the detection method

Quantitative estimation of the occurrence of microorganisms not only presupposes a detection method that is sufficiently sensitive (i.e.: the threshold must lie below the number of microorganisms), but also a known recovery. This means that the fraction of organisms that is lost during the processes of concentration and purification, or the fraction of organisms that remain undetected, must be known. Literature data seem to indicate a high degree of spreading for the recovery ratio of pathogenic organisms. The detection of indicator and index organisms can be performed more efficiently. Information is needed as to whether this variation indicates systematic differences between experimental setups, or random fluctuations occurring in any assay. Here, too, point estimates provide little information. Ideally, lots of experimental data from different experimental settings would provide information about the frequency distribution for the recovery ratio. On the other hand, a model description of the assay procedure may enhance the interpretability of the widely varying numeric estimates.

3.2 Viability of organisms to cause infection

A problem occurring with the estimation of exposures to pathogenic microorganisms is that not every organism that is swallowed may be alive and capable of initiating infection in the host. In the end, the viability of an infectious organism can only be determined in the actual host it may infect. Since this obviously cannot be used to set up an assay, an alternative host cell or organism must be found. For viruses, detection is usually based on some physiological interaction with a living cell, often resulting in cell death. Bacterial tests often use some function of the bacterial metabolism for their detection, thereby also providing some information on their physiological integrity. The predictive value of these assays for the virulence of the bacteria is questionable, however: culture media are artificial, and factors necessary for human infection are not assayed. With respect to protozoans, physical detection and functional features like infectivity are two separate properties. Cysts or oocysts devoid of inner structures may still be labeled with antibodies. The presence of morphological features like nuclei may say something about the infectivity; an empty shell can be assumed to have lost the potency for infection. More reliable information can only be obtained via in vitro excystation or infection of animal models, like neonatal mice (Finch et al., 1993a; Finch et al., 1993b).

An example from drinking water monitoring practice with possible protozoan contamination may illustrate the importance of recovery and viability estimates for the estimated health risks:

> ...in order to arrive at the actual concentration of pathogens, the recovery of the applied method for the determination of the (oo)cyst concentration must be estimated. Moreover, not every (oo)cyst appears to have retained its potency for infection throughout the treatment process. When R is the fraction of (oo)cysts recovered for counting, and I the fraction of viable (oo)cysts, the actual dose of infectious particles is found by multiplication with a correction factor I/R. The following ranges are assumed to apply:
>
> **Infectivity** between 3% and 100%, most probable value 30% (LeChevallier et al., 1991).
>
> **Recovery** between 1% and 30%, most probable value 5% (compiled from various sources by G.J. Medema).
>
> If we take these ranges as the margins of a (95%) confidence interval, and both I and R are Log-normally distributed[1], the parameters of these distribution functions may be estimated, and used to construct a confidence interval for the ratio I/R (see section 5.1.2): About a median ratio 6 (see also (Regli et al., 1991)), a confidence interval ranges between 0.857 and 42[2] (cf. figure 3.1) ...

[1]This seems to be a reasonable assumption: the presumptive nominal values are close to the geometrical means of the corresponding range margins (at least closer than their arithmetic means), and both I and R cannot have negative values, whereas their log transforms can.

[2]The Infectivity I ranges between 3% and 100%. An uncertainty factor(Slob, 1994) of 3 with respect to the median value (30%) produces a suitable interval. This leads to $\mu_i = 3.4012, \sigma_i = 0.560$. R varies between 1% and 30%. Variation with a factor 5 about the median (5%) leads to $\mu_r = 1.609, \sigma_r = 0.821$. When m is the median of the resultant distribution (figure 3.1): $\log m = \log 30 - \log 5, m = \frac{30}{5} = 6$. When v is the uncertainty factor of the resultant distribution, then $(\log v)^2 = (\log 3)^2 + (\log 5)^2, v \approx 7$.

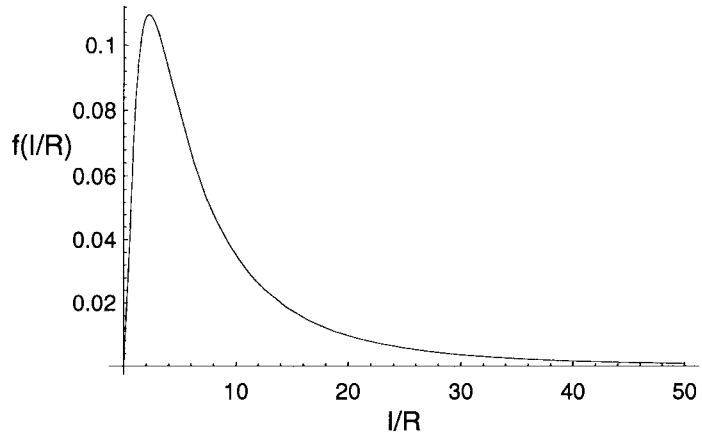

Figure 3.1: Probability density function for the ratio I/R, under the assumption that both I and R are distributed log-normally.

3.3 Spatiotemporal distribution

The growing interest in quantitative microbial risk assessment has increased the need for reliable information about the spatial and temporal distribution of microorganisms in water. When the distribution of a pathogenic organism in a certain body of source water, and its variability in time, are known, better assertions can be made with regard to both expected values and range of the number of organisms in a sample of a given size. Ultimately, we are interested in the frequency distribution of the organisms in the consumed water. As stated above, the only way to obtain detailed information like this in finished water, is via predictive modeling of the modifications the treatment process imposes on the raw water distribution.
With respect to risk assessment, there is great need for data concerning the temporal and spatial distribution of microbial organisms in the whole production chain for drinking water: source water, treatment process, treated water, the distribution system, and consumer's tap water. Available information on the occurrence of microorganisms in water samples indicates that deviations from randomness are quite common (Pipes et al., 1977). The aggregation of organisms, or their association with particulate matter should receive attention, because this may significantly alter both their sampling distribution (Haas and Heller, 1990; Maul et al., 1993) and their sensitivity to chemical disinfectants (Sharp, 1976).

Returning to our example of a case of possible contamination with protozoan (oo)cysts:

> ...in a case of possible contamination, a single measurement is available for the raw water concentration of *Cryptosporidium*: 70 oocysts per 100 l. When this figure is compared with literature data (LeChevallier and Norton, 1993) for a somewhat similar water production plant (site 3 in (LeChevallier and Norton, 1993)), it appears to lie near the center (median) of the measured distribution of concentrations. If the same distribution would be valid for the present case, 95% of occurring (oo)cyst concentrations would be below 5 / l, or 500 / 100 l. A conservative estimation of presumptive peak concentrations would thus amount to five-fold the

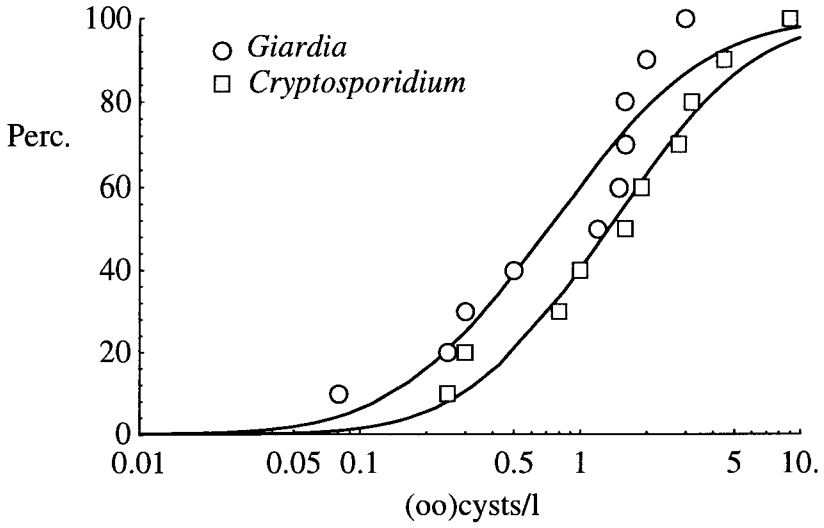

Figure 3.2: Cumulative distribution of *Giardia* and *Cryptosporidium* (oo)cysts in a Canadian watershed, with raw water withdrawn from a dammed reservoir. Data from (LeChevallier and Norton, 1993). The drawn curves are lognormal cdf's, fitted to these data.

measured incidental concentration ...

Whenever there are strong temporal fluctuations in the pathogen content of the water supply, the moment of water intake may influence the probability of infection. This might especially be important for exposure assessment of protozoan (oo)cysts, where the source contamination has been shown to fluctuate in a spiking pattern. Prolonged periods with a very low concentration are followed by peaks of high concentration but short duration (Poulton et al., 1991; Ketelaars et al., 1994). In this case, the risk of infection will show large variations in time. Periods of negligible risk would be interspersed with periods of high risk, in which water intake is coincident with the occurrence of a peak in pathogen content. In an attempt to account for such complications, the use of the geometric mean has been proposed instead of the arithmetic mean (Rose and Gerba, 1991) to calculate the accumulated risk over prolonged exposure periods (see also section 5.1.3). This avoids overestimation of concentration peaks of short duration. Although such a procedure may better reflect the overall risk of the population in some cases, this is not necessarily true in general. More detailed information about the temporal pattern of fluctuations in occurrence of these organisms would provide a firmer basis for the use of point estimates like this.

Returning to the example of *Cryptosporidium* contamination:

> ...the cumulative distribution in figure 3.2 is fitted well by a log-normal cdf. This seems to be in agreement with observations by (Rose and Gerba, 1991), who report that over a 40 day sampling period only 10% of the samples contained more than 100 cysts/100 l, whereas in 60% of the samples no cysts were detected in 100 l...

3.4 Consumption of unboiled drinking water

Finally, some attention must be given to the amount of water an individual consumes in a certain period of time. Unfortunately enough, not very much is known about the consumption of drinking water that has not been boiled (tap water, used in squash, ice cubes in various drinks, teeth brushing, medicines, etcetera) in the Netherlands. A single estimate has been given in the results of a survey (Haring et al., 1979): 0.25 l/person daily.
A detailed study of the distribution of water intakes among different subpopulations in a large survey in the United States has been published recently (Roseberry and Burmaster, 1992). Within each subpopulation, and over the complete population as a whole, the individual water intake appears to be fitted well by the log-normal distribution. Interestingly enough, the uncertainty factor (95 % confidence interval) appears to be approximately equal to 3 both for the population as a whole, and for every individual subgroup that was investigated. Therefore, pending specific studies, we propose to use this same variation factor for the estimation of uncertainty in risk estimates for the Netherlands.
The *timing* of water intake might also be relevant for risk calculations. If most people consume a lot of unboiled drinking water in summer, but do less so in winter, the daily risk on a summer's day will be higher than that on a cold day in winter. The concentration of pathogenic microorganisms may well show seasonal variation as well. Ideally, information on both sources of variation should be employed for assessment of the long term health risk.

3.5 Research needs

Develop a database for pathogenic and toxigenic microorganisms in water. The impact of treatment and the influence of different environmental conditions, such as microbial clumping and association of microbes with particulates, need to be included.
Furthermore, the influence of water treatment procedures on the virulence of pathogenic organisms awaits detailed research. The physical state of organisms (aggregated, associated with suspended particles), and their physiological state (stressed, injured) may influence both their detectability, and the probability of their causing infection.
Finally, more information is needed about unboiled drinking water consumption behaviour in the Netherlands, with regard to different subpopulations (age, health state, profession, etc.), as well as for the population as a whole.

Chapter 4

Dose-response relationships

The possible events taking place when contaminated water has been consumed, are listed schematically in figure 4.1. The occurrence of successive stages in this process may be described as a chain of conditional probabilities.

1. When water containing a low concentration of pathogenic microorganisms is ingested, there is a certain probability that one or more of these organisms are swallowed:

   $P_{exp}(j \mid \mu)$ = Probability that j pathogenic organisms are ingested, when a mean dose μ was present.

2. Once they have entered the intestinal tract, these microorganisms may cause infection: multiplication of the organism within the host, resulting in the excretion of new organisms into the environment:

   $P_{inf}(infection \mid j)$ = Probability of developing infection provided j pathogenic organisms have been swallowed.

3. Infection may proceed to cause symptomatic disease:

   $P_{ill}(illness \mid infection)$ = Probability of becoming ill provided the host is infected.

4. A few illness cases may ultimately lead to death of the host[1]:

   $P_{dth}(death \mid illness)$ = Probability of dying provided the host is ill.

Waterborne diseases usually involve exposure to pathogenic microorganisms at doses that are too low to obtain dose-response data via direct experiments. This would require a much too large number of trials (exposed hosts). Therefore, risk assessment procedures have to start from dose-response data at (relatively) high doses, like those obtained in experiments with human volunteers. Then a mathematical model is fitted to these data, and the mathematical relationship is employed to extrapolate response probabilities to the low doses, prevalent in drinking water samples.

[1] Especially in susceptible subpopulations (YOPI's: young, old, pregnant, and immunocompromised individuals)

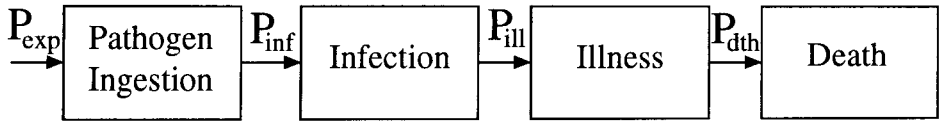

Figure 4.1: The cascade of events that may take place upon exposure to contaminated drinking water (modified after (Haas et al., 1993)): At a certain mean concentration of pathogenic microorganisms in the consumed water, there is a probability $P_{exp}(j)$ of swallowing a certain number j of organisms. These will cause infection (by some standard, like excretion of newly grown specimens, or seroconversion) with probability P_{inf}. Once infected, a person may develop symptoms (P_{ill}), and an ill person may eventually die (P_{dth}).

4.1 Black-box approach

If we assume infection to occur when colonization of the gastrointestinal tract causes the shedding of newly grown organisms from a host, the processes leading to infection may be viewed upon in two different ways. If there is a threshold, the joint action of more than a single pathogenic microorganism may be needed to develop infection. On the other hand, each microorganism may be acting by itself, independent of the others invading the host. However, the infectivity of a single organism may be low, so that exposure to more than a single specimen is necessary to produce an observable response. At the level of the observer, distinction between these two mechanisms may thus remain unclear (Armitage et al., 1965).
In a key paper on the estimation of infection risk at low doses, Haas compares three dose-response models (Haas, 1983): the **log-normal** model, the simple **exponential** model, and the **beta-poisson** model.

4.1.1 Log-normal model

Whenever a variable is the result of the multiplication of a large number of mutually independent stochastic variables, this variable will be distributed lognormally. If the resistance of a host to a pathogenic microorganism results from successive operation of many independent processes, each contributing with a certain factor, a threshold for infection among a population of hosts will be lognormally distributed. If the individual minimal infective doses within a population are log-normally distributed, the fraction of responding individuals will also be distributed log-normally. Conversely if, in the absence of a threshold, the infectivity of pathogenic organisms results from a large number of independent factors, the probability of infection will also follow a lognormal distribution:

$$P^* = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Z} e^{-\frac{1}{2}z^2} dz \tag{4.1}$$

$$Z = \frac{\log \mu - \mu_n}{\sigma_n} \tag{4.2}$$

P^* is the probability that a single individual exposed to a dose of μ pathogenic organisms will develop the response (become ill or infected) (Haas, 1983). The parameters

μ_n and σ_n define the log-normal distribution.

4.1.2 The exponential and the beta-poisson model

The single hit or simple exponential model and the beta-poisson model both start from the assumption that the development of infection may be described as a two-stage phenomenon. First, the host must be exposed to one or more pathogenic organisms. Subsequently, a fraction of these organisms causes infection. Not all ingested organisms reach a target site where they can initiate a response, because they may not be viable, they may be inactivated by decay, or their activity may be impaired due to host defences. Hence, the occurrence of an individual response is governed by two probabilities. The probability of exposure to say j pathogenic organisms: $P_{exp}(j)$. And the conditional probability of k surviving pathogenic organisms, from j organisms that have entered the host, $P_{sur}(k \mid j)$.
When the probability for a single pathogen to survive and reach its target is independent of the presence of other pathogens, and the magnitude of this probability is r, $P_{sur}(k \mid j)$ follows a binomial distribution:

$$P_{sur}(k \mid j) = \binom{j}{k} r^k (1-r)^{j-k} \tag{4.3}$$

when there is no mutual dependence between organisms.
If we assume that for infection to occur, at least k_{min} organisms must survive within the host:

$$P_{inf}(k \geq k_{min} \mid j) = \sum_{k=k_{min}}^{j} P_{sur}(k \mid j) = \sum_{k=k_{min}}^{j} \binom{j}{k} r^k (1-r)^{j-k} \tag{4.4}$$

The (unconditional) probability of infection, with a given exposure distribution:

$$P^*_{inf} = \sum_{j=k_{min}}^{\infty} \sum_{k=k_{min}}^{j} P_{exp}(j) P_{sur}(k \mid j) \tag{4.5}$$

These probabilities have been evaluated for a few cases:

- When microorganisms are distributed randomly within a water volume, $P_{exp}(j)$ follows the Poisson distribution.

  $$P_{exp}(j) = \frac{\mu^j}{j!} e^{-\mu} \tag{4.6}$$

  where μ is the average number of organisms per exposure event.

  The case for Poisson distributed exposures and a constant probability of infection, r, per ingested organism, has been evaluated for Tobacco Mosaic Virus (Furumoto and Mickey, 1967). If the minimal number of pathogen particles at the target site necessary for response, k_{min}, is assumed 1, the probability of response can be shown to equal:

  $$P^*_{inf} = 1 - e^{-r\mu} \tag{4.7}$$

  This dose-response relationship is referred to as the (simple) **exponential model**.

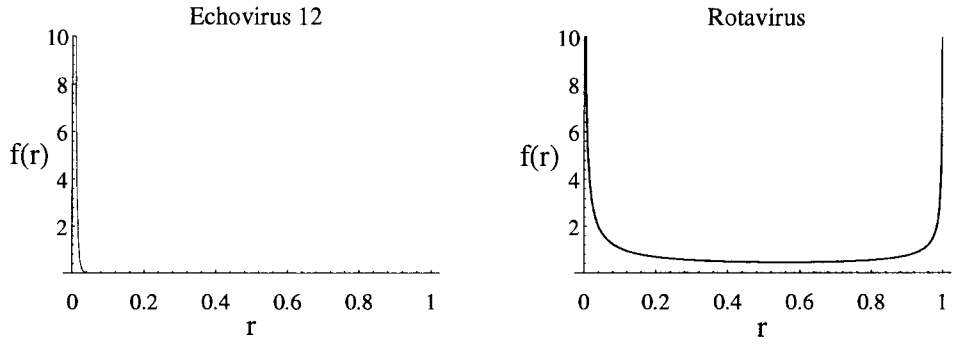

Figure 4.2: The shape of the (beta-) distribution for r, the probability of infection per ingested particle. Two typical cases are shown. Left Echovirus 12: $\hat{\alpha}$=0.374, $\hat{\beta}$=186.69 (Regli et al., 1991). Note that r is small for most of the ingested organisms. Only a very small fraction of the population experiences a high probability of infection. This may point to either a small fraction of viable organisms reaching a target site, or high susceptibility in only a small proportion of the host population. Right Rotavirus $\hat{\alpha}$=0.26, $\hat{\beta}$=0.42 (Regli et al., 1991). Here the probabilities of either high or low values of r are elevated, compared to those of intermediate values.

- The assumption that the probability of infection/disease per ingested particle only attains a single, discrete value, may not be very realistic. If r follows a frequency distribution $f(r)$, a range of pathogen-host interactions may be modeled, instead of a single possible event. In this case, the probability of infection/disease is found by taking the integral over all r-values, thereby producing a contagious distribution:

$$P^*_{inf} = \int_0^1 (1 - e^{-r\mu})\, f(r) dr$$

Furumoto and Mickey have considered the case where $f(r)$ is the probability density function of the Beta-distribution, which exists only on the interval { 0,1 } (Furumoto and Mickey, 1967). This pdf:

$$f(r) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} r^{\alpha-1}(1-r)^{\beta-1}$$

is characterized by two parameters α and β, and can take on a wide variety of shapes. Figure 4.2 shows an example. It can be shown (Furumoto and Mickey, 1967) that, if $\beta \gg \alpha$, the probability of infection may be approximated as:

$$P^*_{inf} \approx 1 - \left(1 + \frac{\mu}{\beta}\right)^{-\alpha} \tag{4.8}$$

which defines the dose-response curve of the **beta-poisson model** (Haas, 1983). In practice, this model relation has also been used with data sets producing parameter combinations that did not satisfy the condition $\beta \gg \alpha$, see e.g. figure 4.3.

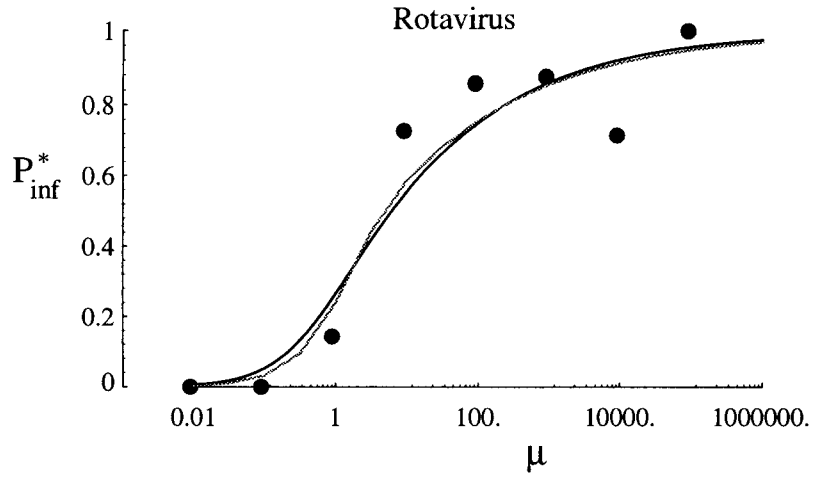

Figure 4.3: Data of (Ward et al., 1986) for the probability of infection from Rotavirus, with the dose-response curve as predicted by the Beta-Poisson model (MLE estimates $\hat{\alpha} = 0.26$, $\hat{\beta} = 0.42$). The grey line illustrates the best fitting curve (MLE estimates $\hat{\alpha} = 0.223$, $\hat{\beta} = 0.448$) obtained by direct numerical integration of the dose-response integral, without the simplifications provided by Furumoto and Mickey (1967). The parameter values found with these data are outside the region within which these simplifications are valid ($\beta \gg \alpha$).

With some experimental dose-response data sets, the exponential model equation provides good fits. Often however, the slope predicted by the exponential model for the relationship between P^*_{inf} and μ is too steep to fit the data well (Gifford and Koch, 1969). The beta-poisson model equation appears to fit well to almost all data sets available at present.

4.1.3 Applications

In a comparative study, (Haas, 1983) the three models mentioned above were tested with a number of data sets from the literature. Goodness of fit was compared using a χ^2 criterion for the likelihood ratio. The conclusions are quoted here, because they still remain relevant:

1. The beta-distributed stochastic model of microbial dose-response curves fits data of as many organisms at least as well as the log-normal deterministic model.
2. Based on the satisfactory fit of the beta model[2] to much data, it is impossible to rule out the hypothesis that one organism, when ingested, can cause infection and/or disease in at least a portion of the exposed population; to rule out such a hypothesis, data taken at very low microbial doses are required.

[2]Or other model equations

3. The extrapolated risks from the stochastic model to low doses are in excess of those values from the log-normal model, when both classes of models are found to provide a satisfactory fit to the data. Thus, the use of the stochastic type of model provides a conservative estimator of risk associated with low dose exposure in comparison with the log-normal model.

Low dose data would be necessary to discriminate between deterministic and probabilistic models, because it is in this range where the models show the largest differences. For any dose-response model to be used for actual risk assessment, some form of uncertainty analysis should be carried out.

An example of the construction of a confidence interval for the protozoan parasite *Giardia* with the exponential model is given below:

> ...Published values (Regli et al., 1991; Haas et al., 1993) for r, the probability of infection per ingested particle, have been inferred from dose-response data obtained for infection of volunteers with *Giardia* by Rendtorff (Rendtorff, 1954):

i	N (oo)cysts	T_i exposed	I_i infected
1	1	5	0
2	10	2	2
3	25	20	6
4	100	2	2
5	10^4	3	3
6	10^5	3	3
7	3.10^4	3	3
8	10^6	2	2

> Log-likelihood ratio (Haas et al., 1993):

$$\ell = -2\sum_{i=1}^{k}\left\{I_i \log\left(\frac{I_i}{T_i\pi_i}\right) + (T_i - I_i)\log\left(\frac{T_i - I_i}{T_i - T_i\pi_i}\right)\right\}$$

$$\pi_i = 1 - e^{-r\mu}$$

> Using the data given above, the variation of ℓ with r can be calculated. The log-likelihood ratio can be shown to follow a χ^2 distribution, with k-1 degrees of freedom (k groups of data). This property is used for the construction of a confidence interval. At the 95% level, the confidence interval for r is: $0.008 < r < 0.042$ ...

4.2 Further modelling

When a pathogenic microorganism has been swallowed, and it succeeds in reaching sites within the gastrointestinal tract that are suitable for colonization, its success in doing so will depend in part on its growth rate. The response of the host, activation of the defence system, will also involve a certain rate of increase. For this reason, a possible direction to proceed to more mechanistic types of models may be that of the birth-death models (Armitage et al., 1965). Here, the time dependent processes of growth and decay are included in the model, thereby also introducing more parameters. Hence, future

work may proceed into this direction, if this should be warranted by either new data on exposure characteristics within the host, or new experimental data on dose response relationships.

For the low exposure range, the range of interest to health authorities, the existence of a threshold dose below which no effect occurs is often postulated. Although this now seems unlikely from a biological point of view, the complex internal (immunological) response of the human body may promote the existence of a level below which no response is apparent[3] (McMichael, 1989). Setting up a model for the development of end effects beyond the stage of infection: various symptoms from short term acute sickness to chronic effects, may require to take such strongly nonlinear phenomena into account. Reliable dose-response data are very hard to obtain, often only in expensive experiments. For a number of pathogenic organisms that cause chronic illnesses, or those with a high mortality, experiments with human volunteers may even be considered unethical. If the use of animal experiments would be possible, a potentially much larger reservoir of experimental data would become available. In addition, experiments that constitute a high level of risk for the participants would at least impose less severe ethical problems.

An opportunity that might arise with the use of animal models, is the comparison of attack rates for different subpopulations. It is conceivable that comparison of experimental data from normal and immunocompromised animals may tell something about differences between such conditions in the human population.

The dose-response models listed above do not account for interspecies differences, or translation of results to other species. A possible alternative approach to the dose-response problem might proceed analogous to procedures developed for the toxic effects of noxious substances, especially those without a response threshold, such as mutagenic or carcinogenic compounds. Here laboratory experiments are performed with animals, and the results are extrapolated to human subjects, using (more or less) standard procedures.

Adjustments are made for interspecies differences in body size, lifespan, and basal metabolic rate[4], and adjustments to account for the difference between high doses administered to animals, and the low doses to which humans are likely to be exposed. A problem arising with respect to pathogenic microorganisms is the possibly much more specific interaction between the host and the hazardous agent.

In the future it may be possible to incorporate knowledge from mathematical models of e.g. the immune response and pathogen multiplication inside the host organism, and arrive at a more or less complete model description of the infection-disease-mortality chain of events.

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[3]Note however, that since the absence of an event can never be proven within an empirical predicament, this line of reasoning bears little significance for the prediction of health problems.

[4]For carcinogenic chemical substances standard procedure includes (AWWA, 1993) screening bioassays at the maximum tolerated dose (MTD), and one lower dose in at least two species of rodents. Data from the species and sex with the highest risk are taken, using the 95% upper confidence limit of the linearized multistage model (LMS model, or an alternative model), and applying a body-weight-to-surface-area correction or not.

4.3 Research needs

Research needs for the development and testing of reliable dose-response models:

- dose-response data, preferably at well known doses, with high numbers of exposed individuals.
- dose-response data for different subpopulations, especially those with impaired immune systems
- clinical illness and mortality rates for important pathogens and toxigenic microbes.
- development of a standard typology for clinical illnesses.
- the impact of different routes of exposure.
- the influence of timing and duration of exposure.
- collect data on the occurrence and sensitivity of compromised individuals in populations exposed to pathogenic and toxigenic microbes. Determine the virulence and other pathogenesic factors of waterborne microbes, especially for opportunistically pathogenic microbes, and the mechanisms by which waterborne pathogens subvert host defences to cause infection and disease.

Chapter 5

Risk characterization and management

5.1 Risk characterization

The US Environmental Protection Agency defines risk characterization as follows (National Academy of Sciences, 1983):

> Risk characterization is the process of estimating the incidence of an adverse health effect under the various conditions of human exposure described in exposure assessment. Risk characterization is performed by combining the exposure and dose-response-assessments.

Summarizing the approach used so far, the procedure has been:

- determine the organism of interest
- estimate consumer's exposure by multiplying estimated concentrations (of the organism in question in the consumed water) with the estimated amount of consumed water (whether or not split for different subgroups).
- Find appropriate dose-response data and evaluate in terms of model equations, in order to enable extrapolation to the low dose range of actual exposures.

When quantitative estimates of both the exposure and the dose-response relation are available, the risk of occurrence of the considered end effect can be calculated. As soon as a risk estimate has been determined, its acceptability may be evaluated.
To do this, the uncertainty in the estimated risk level should be accepted first. If the confidence range is too wide to allow clear and unambiguous decisions, the source of uncertainty must be identified and, if possible, its influence must be minimized. This may imply application of alternative dose-response models, the use of more or other dose-response data, acquisition of more exposure data, or improvement of detection methods.
Secondly, when the risk estimates have been thoroughly established, they may be checked against desired limits.
Finally, compound risk estimates may be calculated by combining the risk from different hazard sources (viral, bacterial, parasitological, chemical). When different risk

sources are coupled, like pathogen content and DBP's, a weighing formula may be composed. This would allow a direct comparison of the effects of different harmful substances and organisms. On the other hand, the estimation of risks from compound sources may in some cases offer an opportunity to minimize the overall risk by manipulating the contributions from the component agents.

5.1.1 Calculation of risk

In many cases, risk evaluations start from the assumption that the dose-response relationship is approximately linear at low doses. Calculation of the risk of infection then simply consists of multiplying the dose estimate with the slope of the dose-response relation at low doses.
Expanding the exponential dose-response relation in a power series in μ:

$$P^*_{inf} = 1 - e^{-r\mu} = 1 - \sum_{i=0}^{\infty} \frac{(-1)^i r^i}{i!} \mu^i = 1 - 1 + r\mu - \frac{r^2}{2}\mu^2 + \ldots$$

For small values of μ, the mean number of organisms per exposure event:

$$P^*_{inf}(\mu) \approx r\mu$$

Similarly, for the beta-poisson dose-response function:

$$P^*_{inf} = 1 - \left(1 + \frac{\mu}{\beta}\right)^{-\alpha} = 1 - \sum_{i=0}^{\infty} \frac{(-1)^i \Gamma(\alpha + i)}{i!\beta^i \Gamma(\alpha)} \mu^i = 1 - 1 + \frac{\alpha}{\beta}\mu - \frac{\alpha(\alpha+1)}{2\beta^2}\mu^2 + \ldots$$

Leading to the low dose extrapolation for the beta-poisson model:

$$P^*_{inf}(\mu) \approx \left(\frac{\alpha}{\beta}\right) \mu$$

An example of the calculation of the risk of infection with protozoan (oo)cysts, for which various data have already been given (chapters 3 and 4), is given in the next section.

5.1.2 Uncertainty analysis

In the previous section, the risk of infection was calculated by multiplying a number of values, each one a point estimate by itself. The reliability of the risk estimate depends very much upon the reliability of these constituting factors. Ideally, we would like to have a frequency distribution for every variable that enters the calculation. Then the frequency distribution of the resulting probability of infection (or disease, or death, if sufficient information is available) could be assessed, either via analytical methods, or via Monte Carlo procedures.
Usually, very little is known about frequency distributions of the variables in our risk calculation. As a first approximation, we therefore assume that all values are distributed log-normally. Presently, the lack of knowledge concerning exposure estimates does not offer strong arguments to favor alternative distributions. This simplification does offer a great advantage: the uncertainty in the end result can be calculated quite easily. When

a variable is distributed log-normally, the log transform of this variable is distributed normally. When a stochastic variable X is calculated by adding a number of mutually independent stochastic variables, each with a normal frequency distribution, the frequency distribution of X will again be normal, with mean value equal to the sum of the individual means, and variance equal to the sum of the individual variances:

$$X_i \sim N(\mu_i, \sigma_i),$$

$$X = \sum_i X_i \sim N(\mu, \sigma)$$

$$\mu = \sum_i \mu_i,$$

$$\sigma^2 = \sum_i \sigma_i^2$$

When a number of variables Y_i, all with a log-normal frequency distribution are multiplied, to calculate a variable Y, then:

$$\log Y_i \sim N(\mu_i, \sigma_i)$$

$$Y = \prod_i Y_i,$$

$$\log Y = \sum_i \log Y_i \sim N(\mu, \sigma)$$

Any linear shift on the log transformed scale translates into multiplication with a certain factor on the linear scale. This offers the opportunity to calculate an uncertainty measure by quite simple means. Since there is a proportional relationship between the standard deviation of the normal distribution and, say, the 95% point (1.96σ), a confidence region may be calculated directly from such an "uncertainty factor" (Slob, 1994):

$$\log v = \sqrt{\sum_i (\log v_i)^2}$$

where v and v_i are uncertainty factors in the end result and the constituting factors, respectively.
A more thorough treatment of this approach may be found elsewhere (Slob, 1994).

Returning to our sample calculation of the risk of infection with a parasitic protozoan for drinking water from a conventional surface water treatment plant:

> ...the uncertainty in the calculation of risk at subject level may be evaluated by assessing confidence intervals.
>
> - The risk of infection per ingested (oo)cyst. Most probable value for *Cryptosporidium* (based on Maximum Likelihood Estimation) $\hat{r}$ = 0.005 . 95% confidence interval (based on χ^2 criterion for the log-likelihood ratio) 0.001 $< r <$ 0.016 (Haas and Rose, 1994).

- The variability in oocyst concentration in the water system has not been measured. In the exponential and beta-poisson models the microorganisms are considered to be poisson distributed. Since at this time the only information we have about the oocyst concentration is a single measured value, there is no firm basis for any additional refinements. To avoid pointless speculation, we may simply change our initial question to: What would be the health risk, caused by a *mean* concentration of 0.7 *Cryptosporidium* oocysts per 100 l drinking water?
- When both the recovery of the detection method and the infectivity of ingested oocysts are log-normally distributed, the distribution of the ratio I/R is also lognormal, with median I/R=6, and uncertainty factor 7, leading to a range $0.857 < I/R < 42$ (see section 3.2).
- In a comprehensive study in the United States, the distribution of the unboiled drinking water consumption was found to fit well to a lognormal distribution, with median $\sim$ 1 l / day and uncertainty factor $\sim$ 3 (Roseberry and Burmaster, 1992). Different subpopulations (age-groups) show large differences in median values, but all share approximately the same uncertainty factor. Unfortunately enough, similar data are not available for the Netherlands. A value of 0.25 l / day has been determined in a Dutch survey(Haring et al., 1979). We might take, as a first approximation, this value of 0.25 l / day as the median of a lognormal distribution with uncertainty factor 3.

The individual daily dose amounts to:

$$\mu = \text{daily water intake} \times \text{measured concentration} \times I/R$$

Insert the numbers inferred above:

$$\mu = 0.25 \times (0.7 \times 10^{-2}) \times 6\times \approx 10^{-2}$$

The daily risk, using linear approximation for low doses:

$$P^*_{inf} = \hat{r} \times \mu = 0.005 \times 10^{-2} = 5 \times 10^{-5}$$

If we leave aside variations in (oo)cyst concentration at the intake site, and consider variations in r, daily water intake, and I/R only, a lower bound for the daily risk would lie a factor 13 below this estimate, hence at 4×10^{-6}. On the other hand, the upper margin would lie a factor 13 above the previous estimate, *i.e.* about 6.5×10^{-4} *per capita* per day.

A more rigorous treatment of the confidence region will require additional data on the exposure level, preferrably monitored over a certain period of time ...

5.1.3 Repeated exposures

Estimates of daily risk may be extrapolated to yearly risk. When P^*_1 and P^*_n are the probabilities of infection after a single (e.g. daily) exposure and after repeated exposures (n times a daily exposure) respectively:

$$P^*_n = 1 - (1 - P^*_1)^n \approx n \times P^*_1 \tag{5.1}$$

as long as $P^*_1 \ll 1$.

Now the yearly risk of infection for our example of protozoan contamination may be estimated:

...if (the previously calculated) concentration would occur in the drinking water during 10 % of the year (e.g. 3 days every month, or one month every year), then the annual probability of infection may be calculated:

$$P^*_{inf} \approx 0.10 \times 365 \times 5 \times 10^{-5} \approx 2 \times 10^{-3}$$

(upper 95 % limit: 2.5×10^{-2}) ...

5.1.4 Secondary spreading

By the definition we have adopted here, any infected individual sheds new pathogenic organisms into the environment. These newly grown pathogens may infect others in the direct surroundings via other pathways, not necessarily related to drinking water. Due to their proximity to this new source, these subjects may be exposed to relatively high concentrations of the pathogenic organism, increasing the probability of becoming infected as well. This phenomenon, which is connected exclusively to microbial health risks, may thus act as a positive feedback system, tending to increase the number of infected or sick individuals following a single infection event. When the secondary infection ratio is known, this amplification factor may be calculated by considering a geometric series (Grubbs et al., 1994). A secondary attack rate ρ causes an initial number of a persons to infect an additional number of ρa persons. These proceed to infect $\rho^2 a$ persons, and so on. The total number of infected persons becomes:

$$a + a\rho + a\rho^2 + a\rho^3 + \ldots = \sum_{i=0}^{\infty} a\rho^i = \frac{a}{1-\rho}$$

When the secondary infection ratio is not much smaller than unity, this mechanism may have considerable impact on the number of infected individuals. The importance of secondary spreading for waterborne outbreaks is not very clear, since epidemiological data cannot be linked very well to exposure estimates, thereby precluding estimations based on quantitative risk assessment. This is an area where more research is needed.

5.1.5 Illness and Death as end points

The probabilities of illness and death are often less well known. For those organisms that have been identified as the cause for a major waterborne outbreak, there may be epidemiological data. Table 5.1 lists estimates for the annual probability of illness and death when the probability of infection is fixed at the level of 10^{-4}, proposed by the USEPA. Values for the risk of dying from waterborne viral disease vary over a wide range, 4 decades, including the risk levels set for various agents in the environment (VROM, 1989). See also section 5.2.

Returning to our exercise for health risks from exposure to *Cryptosporidium*, the possible consequences can be evaluated:

...data from waterborne outbreaks indicate a probability of becoming ill (gastro-enteritis) after infection with *Cryptosporidium* of approximately 40%. If (such) a case of contamination occurred in a city with 100,000 inhabitants, this would cause an increase in incidence of cryptosporidiosis with $10^5 \times 2 \times 10^{-3} \times 0.40 = 80$

Organism	Illness		Death	
	$P(ill \mid inf)$	$P^*(ill)$	$P(dth \mid ill)$	$P^*(dth)$
Astro/calicivirus	10^{-1}	10^{-5}	10^{-6}	10^{-11}
Rotavirus	10^{-1}	10^{-5}	10^{-4}	10^{-9}
Poliovirus	10^{-3}	10^{-7}	10^{-2}	10^{-9}
Coxsackievirus	10^{-1}	10^{-5}	10^{-2}	10^{-7}
Echovirus	10^{-1}	10^{-5}	10^{-2}	10^{-7}
Hepatitis-A virus	10^{0}	10^{-4}	10^{-3}	10^{-7}

Table 5.1: Annual probability of illness and death for waterborne viruses, at an annual risk of infection of 10^{-4}. $P(ill \mid inf)$ and $P(dth \mid ill)$: conditional probabilities (of becoming ill when infected, or dying when ill , $P^*(ill)$ and $P^*(dth)$: unconditional probabilities of illness/death. Approximate data, rearranged from literature (Gerba and Rose, 1993).

cases/year (upper confidence limit 1000). The background level for acute gastroenteritis in the Netherlands has been estimated at 2×10^6 cases/year on a population of 15×10^6. In a city of 100,000 inhabitants, this would amount to about 15,000 cases/year. Approximately 1% (150) of these cases suffered from cryptosporidiosis. Hence, in this hypothetical example, the incidence of cryptosporidiosis would increase by 50%.

Outbreak data have also indicated that the risk of death in a sick person is about 0.01%. For cryptosporidiosis, with a risk of disease of 8×10^{-4}, this leads to a probability of dying of cryptosporidiosis of 8×10^{-8} per person per year. This is somewhat in excess of the risk levels set in (VROM, 1989), see chapter 6 ...

5.1.6 Chemical substances

The concept of risk is well established for chemical substances. An overview of chemical risk analysis is given below to illustrate the procedures, and to show the differences with microbial risk analysis.

For noncarcinogenic compounds, a No-Observed-Adverse-Effect-Level (NOAEL) and a Lowest-Observed-Adverse-Effect-Level (LOAEL) are determined for selected test organisms. The lowest value found (with respect to test species/sex) is used to derive the health based guideline value: this is an estimate of how much daily exposure the human population can tolerate without an appreciable risk of deleterious health effects during a lifetime. For this, the NOAEL or LOAEL is divided by an uncertainty factor. For carcinogens, the results of animal experiments may be extrapolated to humans through the use of statistical models (e.g. the linearized multistage model). See section 4.2.

Maximum-Contaminant-Level-Goals (MCLG's) are then set either by using the RfD, or by estimating a 95% upper limit for a specified excess lifetime cancer risk.

5.1.7 Combining risks from different hazards

When a person is exposed to a mixture of different pathogens, the risk of becoming infected by either of these organisms, or by both, may or may not equal the added risks of either organism by itself. Both synergistic (both attacking the same defense system) and antagonistic (together they invoke a more violent response in the immune system of

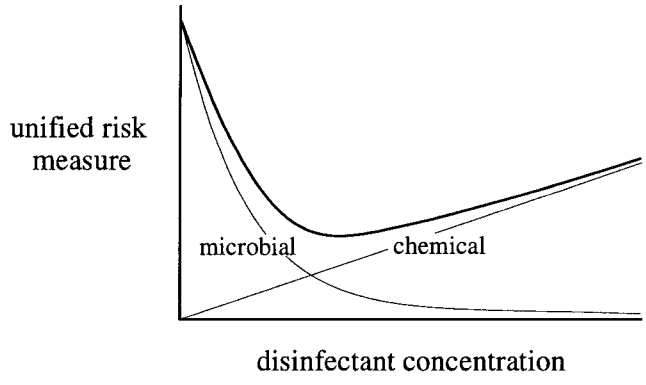

Figure 5.1: Hypothetic risk curve to illustrate the concept of risk minimization

the host) effects are conceivable. With the dose-response information that is available now, no predictions can be made about such effects. At the very low doses normally occurring in drinking water, infection with multiple species of pathogenic organisms may be a very rare phenomenon.
With regard to water treatment by chemical disinfection, there may be the problem of two kinds of risk, competing with each other. An increase in disinfectant concentration kills off a larger proportion of the pathogenic organisms in the water, thereby decreasing the risk of infection and any other end effects. On the other hand, the concentration of disinfection by-products (DBP's) in the finished water will rise, thereby increasing the risk of toxicological problems, or even cancer.
In the case of competing risks, weighing may be performed as illustrated in figure 5.1. In this oversimplified example, additional assumptions are made: the decrease in risk from pathogenic organisms is assumed to be proportional to the decrease in concentration of viable organisms (linear low dose extrapolation). The increase in concentration of disinfection by-products is assumed to depend on the disinfectant concentration in a linear fashion. Finally, a linear low dose extrapolation is also assumed for the risk from these compounds. The shape of such a combined risk curve will also depend upon the choice of unit to express prevailing risks, a problem addressed in more detail in section 6.2. These calculations may have to be differentiated for various pathogens, to accommodate for differences in sensitivity to chlorination, ozonization, etc.

5.2 Risk management

Starting with a straightforward definition of risk management:

> Scientists assess a risk to find out what the problems are. The process of deciding what to do about the problems is risk management.

which positions this stage of the process within the realm of management and political decision making.
Or, using official terminology:

> Risk management ...the complex of judgment and analysis that uses the results of risk assessment to produce a decision about environmental action.

(National Academy of Sciences, 1983) where, for our purposes, environmental action may include those actions aimed at drinking water quality control.
Yet another, alternative definition:

> Risk management ...the process of weighing policy alternatives and selecting the most appropriate regulatory action: integrating the results of risk assessment with social, economic and political concerns to reach a decision

In which there is more emphasis on decision making (Hudson, 1991).
When, in a certain case, an elevated risk level can be estimated with sufficient accuracy, the acceptability of this amount of risk to the exposed population must be determined. In general, this is a task that is performed by the person or organisation responsible for the drinking water quality. Simply speaking, the acceptability of a certain level of risk is performed by checking against preset standards.
These standard levels may be enforced by law, e.g. the SWTR in the U.S., where the level of 10^{-4} for the individual annual risk of infection is stated (Regli et al., 1991), or not. In the latter case, there may be general agreement on a standard level, for instance via analogy with standards in related areas, or by adopting standards from other countries. Problems may arise, however, when risks of unrelated end effects must be compared, see the chapter on risk acceptance and perception (6).
Let us assume for now that there is such a standard for the acceptable level of health risk. When a risk assessment has been made, the result may or may not be acceptable.

If we recall the annual risk of infection in the sample calculation:

> ...the annual probability of infection may be calculated:
>
> $$P^*_{inf} \approx 2 \times 10^{-3}$$
>
> (upper 95 % limit: 2.5×10^{-2}). The US Environmental Protection Agency uses a limit value for the annual risk of infection of 10^{-4} (Regli et al., 1991). Hence, we are a factor 20 in excess of the acceptable limit.

When the estimated risk is less than the standard level for acceptance, a manager may decide that there is room for cutbacks. For such a decision, a well established confidence range for the calculated risk may become important. If, for instance, the drinking water is treated in a number of steps, the robustness of the treatment process may warrant the implication of a safety margin. When there is some knowledge of the performance of the treatment process, for instance a frequency distribution of reduction rates, a rational basis for such a safety margin is automatically built into the risk assessment procedure.
In case the estimated risk exceeds the standard level, the health risk must be considered unacceptable. In practice, this will elicit two kinds of actions (McMichael, 1989): a change in behaviour of the consumers, and, on the other hand, (environmental) countermeasures against the hazard source. When drinking water appears to be contaminated

with a microbial agent, first action consists of informing the consumer population, so that either water can be boiled before consumption, or the consumption of tap water can be avoided completely. For consumers who take such action, the risk of infection may be temporarily abolished. Drinking water managers should keep in mind, however, that such a short term measure could never abolish permanently all risks for the complete population.
In second place, countermeasures on the water management level, like changes in the treatment process (critical control points), or interruption of intake from contaminated sources, take place on a slower time scale, but have a global effect on the consumer population.

5.2.1 HACCP procedures

HACCP or "Hazard Analysis Critical Control Points"(WHO, 1993), is an approach to process management, originally developed for food manufacturing. Originating from quality assurance methodology, HACCP is designed as a sequence of procedures.

1. Assemble HACCP team and put down its terms of reference
2. Describe the product
3. Describe the intended use of the product
4. Construct a flow diagram
5. Verify the flow diagram
6. List all hazards associated with each step
7. Identify Critical Control Points (CCP's)
8. Establish critical limits for each CCP
9. Monitoring for all CCP's
10. Take corrective action when necessary
11. Verification
12. Documentation

For the purpose of the present report, steps 6 - 10 are most relevant, because they are directly related to quantitative risk analysis, and can be used to integrate the results of QRA into process management. A brief outline of the HACCP approach and the relation to QRA will be given. For further details on HACCP, original documents should be consulted (WHO, 1993; FAO/WHO, 1993; Bryan, 1992). The application of HACCP on drinking water supply is surveyed in Havelaar (1994).

Hazard analysis The objective of this step is to obtain a comprehensive list of all biological, chemical and physical agents or conditions which have the potential to cause harm. Some documents on HACCP (ICMSF, 1988; Bryan, 1992) also include the assessment and the severity of the risk associated with these hazards.

Later documents (FAO/WHO, 1993; WHO, 1993) require possible control measures to be defined for each hazard. A control measure can be used to eliminate hazards or to reduce their impact or occurrence to acceptable levels. More than one control measure may be required to control a specific hazard and more than one hazard may be controlled by a specified measure (WHO, 1993). The latter statement is certainly true for drinking water supply. It is increasingly being recognized that safe drinking water supply should not be based on one single barrier such as disinfection, but that a multiple barrier approach is required to effectively eliminate and/or inactivate the various types of hazardous microorganisms. This will also provide an additional safety margin if one barrier would temporarily fail. A large variety of pathogenic microorganisms should be considered for each hazardous situation. Information to set up a list of microorganisms of concern can be derived from a variety of sources:

- outbreaks of drinking water related disease
- outbreaks of diseases associated with recreational waters or shellfish consumption
- foodborne or zoonotic disease outbreaks
- experiments with test animals
- laboratory studies on the occurrence of virulence factors (toxin production, adherence to or invasion of mammalian cells, serotypic or genotypic similarities etc.)

It is necessary to use all sources of information because the information derived from waterborne outbreaks alone is insufficient. In many outbreaks the causative agent is not identified. Moreover, low level endemic diseases are not recognized as an outbreak. However, the actual quantification of the risks associated with a particular microorganism will be more difficult if organisms are not known to have caused outbreaks. The universal nature of drinking water supply makes it possible to produce and update a list of microorganisms of concern at an international level (WHO, 1994). Local information will then be used to decide which organisms actually need to be considered for a particular treatment works.

Identification of Critical Control Points (CCP's) The proper identification of Critical Control Points is a key issue in the HACCP analysis, because the major efforts in process control will be directed towards these steps. In many food processing operations, one single step can be identified that is a major barrier to pathogens, e.g. heating. Chemical disinfection has served a similar role in drinking water production for a long time. Modern concepts in drinking water treatment have changed, however. The acceptable dose for chemical disinfectants is reduced as much as possible to minimize the formation of disinfection byproducts. Newly recognized pathogens, such as viruses and protozoa have a higher resistance to chemical disinfection. As a consequence, other steps are now considered equally important in achieving the final drinking water quality, and the number of CCP's has increased.

Establishment of critical limits for each CCP Critical limits are defined as values which separate acceptability from non-acceptability. As presently used in food

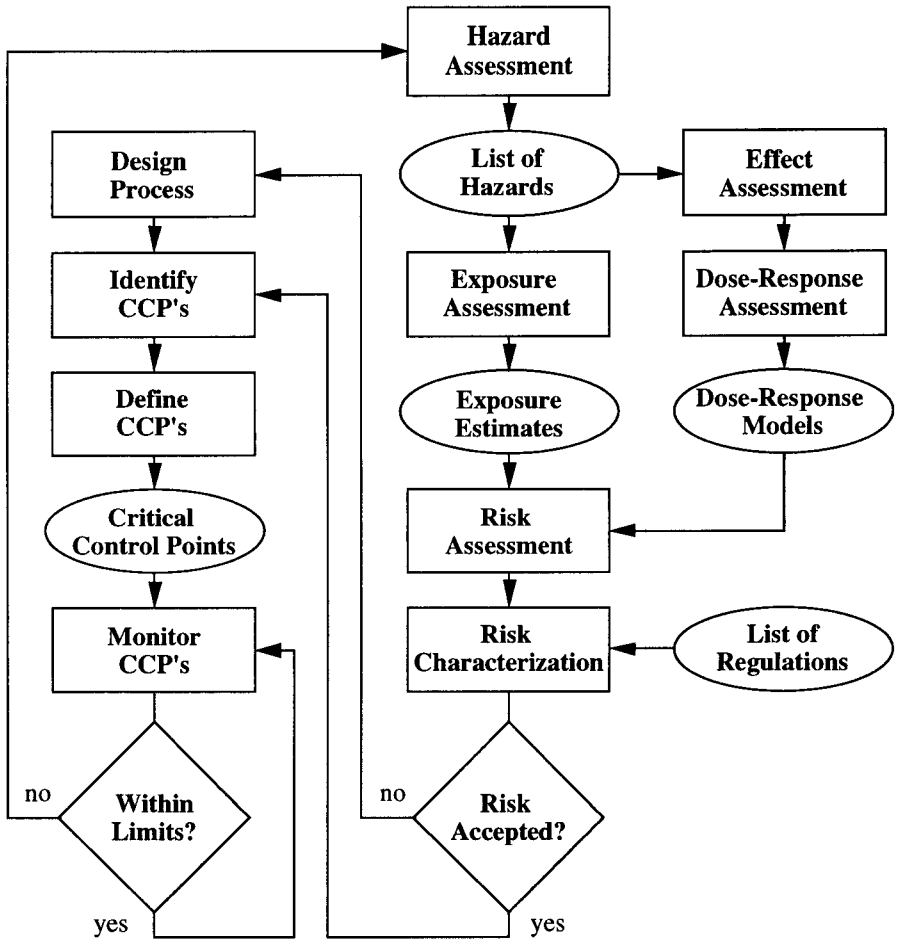

Figure 5.2: Information flow chart for the incorporation of quantitative risk assessment into HACCP based process management. At the left, design of the treatment process is followed by identification of CCP's, after which operational definitions can be formulated. During the design phase, risk assessment may be utilized for proper identification of CCP's. At the right, the risk assessment process chain is given: a list of hazards is set up, for each potentially hazardous organism a dose-response relation is needed, and the actual concentrations the consumer may be exposed to must be determined. The risk estimate is calculated and checked against existing limits. In case of acceptance, the risk assessment data may aid in identifying CCP's. When the estimated risk is unacceptable, the treatment process has to be adapted. After this, the whole process can be repeated. When the process is running, CCP's are monitored continually. As soon as any CCP exceeds its limit value, counter measures can be taken. At the same time, quantitative risk assessment may then be used to evaluate possible consequences.

microbiology, the definition of critical limits is mainly qualitative, and may be subjective. The incorporation of QRA in the decision making process may make HACCP more objective. In principle, a risk assessment should be made for each pathogen identified in the hazard analysis. It may, however be attempted to select agents of priority, either because of their severe effects on human health, or because of their resistance in water treatment. The QRA process will lead to a mathematical description of the treatment process under consideration, ideally with process parameters as input for the model. In such a case, the model can be used to simulate the effect of variations in the process parameters on the final concentration of pathogens, and the related health risk. This can be used to identify the most critical process parameters, and to define the maximum variation.

Monitoring and corrective actions The traditional way of assuring the microbiological quality of drinking water is by monitoring for a series of bacterial indicator organisms in the end product and to a certain extent in several stages of the treatment process, and taking corrective action if (legal) limits are not met. Recent epidemics of cryptosporidiosis have painfully demonstrated that this approach is no longer valid. The HACCP approach focuses the attention of monitoring on those process parameters that are directly related to the health risk of the final water. Ideally, the monitoring parameters are measured online so that corrective action can be taken by a direct feedback system. The microbiological testing of the end product does not fulfill these requirements, and is therefore not well suited for monitoring purposes. It does continue to have an important role in the verification stage, however.

Chapter 6

Risk perception and acceptance

Guiding principles for the socio-economical aspects of the process of setting standards based on risk limits, are the striving for distributive justice (or equity), and the balancing of costs and benefits (McMichael, 1989).
Critical issues for making decisions concerning the relative weights of different health issues are differences in the severity of the health effects, the certainty with which they can be predicted, timing differences (e.g. delayed effects like the increase in risk of cancer at late stages of life after exposure in youth), and the distribution of the health effects among groups in society (special reference to risk groups like elderly, newborns, pregnant, and immunocompromised individuals).
For a better understanding of the public attitude towards various health risks, and to evaluate the significance of the unbalanced distribution of health risks among the population, socio-economical research is needed (AWWA, 1993):

> To explore the policy implications of using alternative yardsticks to measure and compare diverse competing health risks.
>
> Survey work to elicit citizen values about various disease states, citizen attitudes towards uncertainty and their certainty equivalents for uncertain health risks, and citizen valuations about immediate versus deferred health risks.

6.1 Setting limits for acceptance

Health risks often result from (more or less) voluntary exposure to hazardous situations (participating in road traffic, sporting, alcohol consumption, smoking). Environmental hazards usually are involuntary and uncontrollable for the individual citizen. Therefore, more stringent limits are warranted for the latter class of risk sources. Moreover, environmental risks often imply large scale, low level exposures over prolonged periods. This may result in slowly developing, long term effects. In addition to acute symptoms, exposure to pathogenic microorganisms may also cause diffuse effects, or even chronic illness. Exposure levels may be too low to measure directly, while still producing unacceptable health risks. Furthermore, the individual risk level may be low for the population as a whole, but specific subpopulations may still be at unacceptable risk levels due to specific circumstances.

Subpopulations may be exposed to significantly elevated concentrations of pathogenic microorganisms, as a result of their occupation (sewage workers) or habits like drinking large volumes of water on doctor's advice. Microorganisms may be unevenly distributed in space, for instance in the distribution system. Or their occurrence may be clustered in time, for instance a child born in late autumn or early winter, who may be exposed to elevated levels of microorganisms, compared to the levels in summer. In addition to newborn infants, other subpopulations are more susceptible than the average person: pregnant women, aged persons, those receiving immunosuppressive treatment (organ transplant patients, patients suffering from cancer), and those suffering from immunocompromising diseases.
These risk groups represent strongly varying fractions of the population. Application of the same standard risk level for every risk group may not always be feasible from the drinking water producer's point of view. From a public health authorities' point of view, the guideline is to protect the most sensitive group.
For individuals belonging to groups with a substantially damaged immune response, acceptable safety may only be guaranteed by drinking completely sterilized water. This is a problem that needs public discussion, to reach a general consensus. The role for risk assessment here is to increase public awareness by providing reliable information about risk levels both for the population as a whole, and for specific risk groups. The question of balancing the costs against the benefits is a political issue, and lies beyond the scope of risk analysis. Additional research is needed to try and provide a rational basis for the comparison of unrelated health effects, see section 6.2.
Returning to the actual state of affairs in the Netherlands: the Dutch National Environmental Policy Plan (1989) (VROM, 1989) presents a general framework for the use of risk assessment to establish exposure levels to various hazards. The combined acceptable individual risk of mortality resulting from major accidents, exposure to substances, and radiation may not exceed 10^{-5}/year. For each activity or substance the maximum acceptable individual risk is 10^{-6}/year. The risk to ecosystems is assessed by using predictive models, with acceptable risk levels when minimally 95% of the species is presumed to be unaffected. Negligible levels are set at 1% of maximum acceptable levels. This value is chosen to account for the effects of multiple exposures and uncertainties in the estimated levels.
Currently, there are no specifications for acceptable levels of risk due to microbial contamination. For contaminating substances without threshold concentrations, the risk levels are (VROM, 1989):

> Individual risk per substance (mortality, man): The maximum permissible level is defined as 10^{-6}/year. The negligible level is defined as 10^{-8}/year.
>
> Individual risk for all substances combined (mortality, man): The maximum permissible level is defined as 10^{-5}/year. The negligible level is defined as 10^{-7}/year.

A specific issue which should be addressed here, is the question whether health risks originated from drinking water should be treated separately, as a special case. An evaluation of the relative importance of drinking water based health risk compared to the general risk of gastro-enteritis, indicates that drinking water may be a highly significant source of gastrointestinal disease. In a canadian survey among 300 households up to 35

% of the reported cases of gastroenteritis were estimated to be water-related (Payment et al., 1991). If this still somewhat controversial finding were to be established, the pressure on drinking water quality control will only increase. Any significant decrease in drinking water based health risk will result in a significant decrease in the overall incidence of gastrointestinal disease. There is no reason whatsoever to treat waterborne health risk as a special case, in contrast to the risk of food related infectious diseases. The ubiquitous consumption of tap water only emphasizes the need for special attention with respect to quality management.
In order to enhance public comprehension of the outcomes and limitations of quantitative risk assessment, both the results and the procedures by which these have been derived, must be presented in a clear manner. In addition to mathematical procedures, this includes not only accounts of the origin of used data, but also the methods used for the estimation of uncertain factors (Karstadt, 1988). Accounts must be made for the basic assumptions upon which the model was constructed, the validity of used data for the addressed risk groups, determination of confidence regions, etcetera.

6.2 Comparison of risks from different hazard sources

In order to enable direct comparison of varying health effects, the determination of weighing factors for a wide variety of effects, unifying measures must be defined. A few well known examples include:

- The number of lives lost. This is a very crude measure, without any indication about the life expectancy of the individuals concerned.
- The number of life years lost. Differences in life expectancy are included; death at an early age costs a lot of life years, elderly persons have a short life expectancy left, hence loose fewer life years. Here, differences in non-lethal health effects are not discriminated.
- Quality Adjusted Life Years (QALY's) lost. The severity of non-lethal health effects is incorporated by using a weighing factor. This is a less suitable measure for the comparison of diseases in which the end effect usually comprises disease, and very rarely death, with diseases or substances with a high mortality rate.
- Days of disability. This is a measure that is well suited for the comparison of non-lethal diseases, but less so for acutely mortal events. The comparison of strongly delayed effects with cases of acute illness is also not very well documented with disability days.
- Economic burden. Including the costs of medical treatment, the loss of productivity, etc. . May be compiled from a mixture of previous measures. Serves a specific purpose, especially for politic decision making. Decision makers have to address the question how many resources a community can afford to spend on water quality management. In this respect, estimation of the economical significance may be meaningful. The US Environmental Protection Agency distinguishes between three major categories of costing relationships:

- Benefit-cost analysis to weigh the cost of control against the monetary benefits of control.
- Risk-benefit analysis to weigh the economic benefits of a polluting activity (avoid disinfection or decontamination) against the risks to health and the environment.
- Cost-effectiveness analysis to identify the least-cost solution to achieve a given goal, such as a pollutant discharge standard, provided there is agreement about the desirability of regulation.

For each of these approaches, quantitative risk assessment may provide the necessary quantitative measures of adverse effects.

When relatively certain health effects (gastroenteritis) are to be compared with relatively uncertain effects (cancer), public attitudes towards the perception of risk must be included ("gambling with QALY's"). Such an approach may result in the definition of a "discount rate" (AWWA, 1993) for delayed effects, to account for their less severe appeal (A view expressed by the AWWA (AWWA, 1993)). More sociological research is needed to clarify such a potentially controversial issue.

Chapter 7

Validation and verification

In order to add weight to the results of the modelling exercise outlined in the previous chapters, they must be validated. Let us first assume that all models could be calibrated with satisfactory results. That is: reliable data were available in sufficient amounts, and all model equations could be fitted to these data, at least to a satisfactory degree, as judged by some sound criterion. The result will then be present in the form of a risk estimate, with a confidence range, or perhaps even a frequency distribution.
The assessment of a confidence region, or a frequency distribution, to express the uncertainty of a model calculation is a first condition to validate the considered model. In many cases, where a statistical model exists, a confidence region can be constructed. Estimation of a prevailing risk level is often the result of cascade of steps, each contributing some factor. The end result is obtained by a combination of all these factors, via multiplication or division (Slob, 1994). A problem occurs when there is no model calculation available for a given factor. This may be caused by lack of knowledge about the processes that determine the magnitude of that factor. In some cases, expert-based estimates of nominal values and ranges may provide at least an indication of the uncertainty, see section 5.1.2.
Now, one would like to have access to exposure data of a population, with the corresponding incidence levels for the pathogen in question. If these would be available, it would be a very lucky coincidence indeed. Usually, exposure data are very hard to come by in epidemiological studies. When there is not an outbreak, incidence levels are very low, and correlations with exposures to waterborne pathogenic organisms may be absent or impossible to demonstrate. As soon as a waterborne outbreak does occur, the causative event: a rise in concentration of pathogenic organisms, is already well under way. Therefore, estimation of the exposure at the time the infection occurred usually not possible. Nevertheless, an attempt to verify risk estimates for giardiasis outbreaks in the U.S. produced relatively good agreement between predicted infection rates and actually observed attack rates (Regli et al., 1991).
Only when occurrence data are well established, and confidence intervals are known for both the predicted risk estimate and the measured attack rate, validation is possible in its strictest sense. Much more work will be needed to achieve this.
Often, not even the nature of the causative agent of an outbreak is known with certainty. With time, the number of pathogenic species for which dose-response information and occurrence data are available, will increase. This may offer the opportunity to give a

(crude) estimation of the expected number of cases, e.g. gastro-enteritis, in a population. This may be checked against existing epidemiological data.
For the validation of risk assessment procedures new research projects must be set up. Extensive monitoring of pathogen occurrence at various stages of water treatment procedures, is needed, to check model assumptions about sampling distributions. Dose-response studies for more pathogenic species are needed, to verify the model description, but also to build a database of dose-response relations. And finally, epidemiological studies, with special reference to the determination of exposure levels, will be needed to validate health risk models. The problem of differences in susceptibility among subpopulations should also be addressed via epidemiological methods.
Calibration of related model descriptions, like those of water treatment processes, depends upon data on pathogen reduction in treatment processes and their modifications, regrowth in distribution systems, household plumbing, and possibly point-of-use devices.

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Appendix

Symbols

α, β	parameters of the Beta distribution
$\hat{\alpha}, \hat{\beta}$	maximum likelihood estimates of α, β
$\Gamma(x)$	Gamma function ($\Gamma(n+1) = n!$)
$j!$	$j.(j-1).(j-2)...3.2.1$ ($0! \equiv 1$)
$\begin{pmatrix} j \\ k \end{pmatrix}$	$\frac{j!}{k!(j-k)!}$
log	logarithm (base e)
μ	mean concentration of organisms in the water
$N(\mu, \sigma)$	normal distribution, mean μ, standard deviation σ
P_{dth}	probability of dying
P_{exp}	probability of exposure
P_{ill}	probability of becoming ill
P_{inf}	probability of infection
P^*_{inf}	unconditional probability (of infection)
P_{sur}	probability of survival
π_i	probability of infection according to the dose-response model
$\prod_{i=1}^{n}$	product of a series of n terms (i=1 $\rightarrow$ i=n)
r	probability a single organism infects the host
$\sum_{i=1}^{n}$	sum of a series of n terms (i=1 $\rightarrow$ i=n)
ℓ	log likelihood ratio

Abbreviations

AWWA	American Water Works Association
CCP	Critical Control Point
cdf	cumulative distribution function
DBP	Disinfection By-Products
FAO	(UN) Food and Agriculture Organization
GWDR	Ground Water Disinfection Rule
HACCP	Hazard Analysis by Critical Control Points
LMS-Model	Linearized Multistage Model
LOAEL	Lowest Observed Adverse Effect Level
LWL	Laboratorium voor Water- en Levensmiddelenmicrobiologie
MAC	Maximum Acceptable Concentration
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MLE	Maximum Likelihood Estimation
MTD	Maximum Tolerated Dose
NMP	Nationaal Milieubeleids Plan
NOAEL	No Observed Adverse Effect Level
pdf	probability density function
QRA	Quantitative Risk Assessment
QALY	Quality Adjusted Life Year
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieuhygiëne
SWTR	Surface Water Treatment Rule
THM	Trihalomethanes
TQM	Total Quality Management
(US)EPA	Environmental Protection Agency
VEWIN	Vereniging van Exploitanten van Waterleidingbedrijven In Nederland
VROM	(Ministerie van) Volkshuisvesting, Ruimtelijke Ordening en Milieu
WHO	World Health Organization
YOPI	Young, Old, Pregnant, Immunocompromised

Definitions

Infection occurs when a pathogenic microorganism has entered a host, and succeeds in multiplying and colonizing the target organ(s). For gastro-enteric pathogens this usually involves excretion of newly grown organisms (or spores, or (oo)cysts).

Hazard the source of any negative health effect. This includes exposure to a pathogenic microorganism or a chemical substance. In HACCP practice, the actions leading to such exposures are considered hazards.

Risk can be defined as the potential for the occurrence of unwanted negative consequences of an event. The elements of risk are: a choice of action or loss (voluntary, involuntary), a chance of loss (probability, frequency), and a magnitude of loss (character, extent, timing) (FAO/WHO, 1993).

Individual Risk is the likelihood that a person will suffer a given detrimental effect as a result of exposure to an agent (expressed in probability units per year or related to an average concentration per year) (VROM, 1989).

Group Risk is the likelihood per year that a group of at least a certain size will all be the victim of a single accident (event, contamination) at one and the same time (VROM, 1989).

Risk Group is a section of the population that has been selected as having an increased risk in relation to a specific source or agent (VROM, 1989).

Collective Risk for Ecosystems is the likelihood per year that an ecosystem will suffer a particular deleterious effect as a result of exposure to an agent (VROM, 1989).

Risk Characterization is the process of estimating the incidence of an adverse health effect under the various conditions of human exposure described in exposure assessment. Risk characterization is performed by combining exposure and dose-response-assessments (National Academy of Sciences, 1983).

Risk Management Scientists assess a risk to find out what the problems are. The process of deciding what to do about the problems is risk management ...the complex of judgment and analysis that uses the results of risk assessment to produce a decision about environmental action (Hudson, 1991) ...determining and accomplishing those actions that will reduce risk to the greatest degree, given any particular level of resources (National Academy of Sciences, 1983).